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**BENZOXAZIN-3-ONES AND DERIVATIVES THEREOF AS THERAPEUTIC
AGENTS**

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CROSS-REFERENCES TO RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Patent application Serial No. 60/431,528, filed on December 6, 2002, the teachings of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

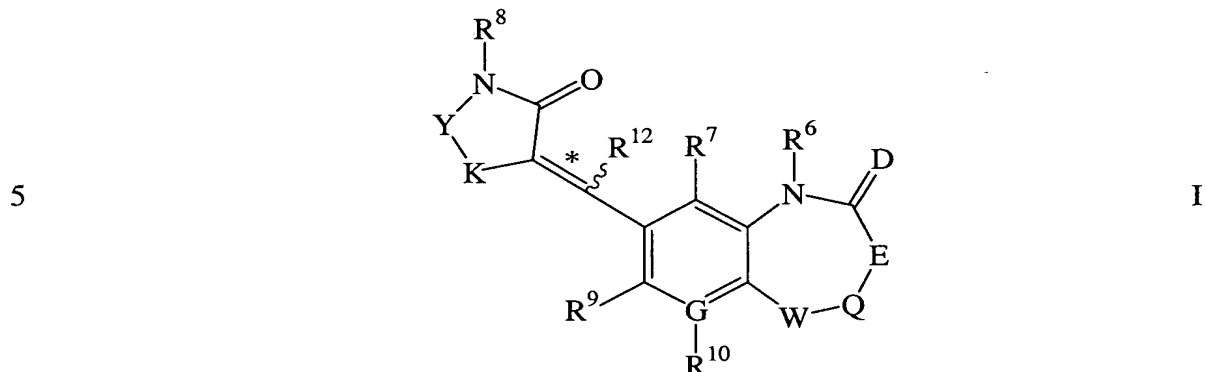
10 Phosphoinositide-3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate phosphoinositols on the 3'-OH to generate PI3P (phosphatidylinositol 3-phosphate), PI-3,4-P₂ and PI3,4,5-P₃. One class of PI3Ks are stimulated by growth factors (Katso et al. *Annu. Rev. Cell Dev. Biol.* 2001;14:615-675) and include PI3K α , PI3K β , and PI3K δ (Vanhaesebroeck et al. 15 *Proc. Natl. Acad. Sci., U.S.A.*, 1997;94:4330-4335; Katso et al., 2001). A separate class of PI3Ks are activated by G-protein coupled receptors and include PI3K γ . The growth-factor stimulated PI3Ks (e.g., PI3K α), have been implicated in cellular proliferation and cancer (reviewed in Katso et al., 2001; and Vivanco and Sawyers *Nature Reviews*, 2002;2:489-501). PI3K γ has been demonstrated to be 20 involved in signaling cascades. For example, PI3K γ is activated in response to ligands such as C5a, fMLP, ADP, and IL-8. In addition, PI3K γ has been implicated in immune diseases (Hirsch et al. *Science* 2000;287:1049-1053). PI3K γ null macrophages show a reduced chemotactic response and a reduced ability to fight inflammation (Hirsch et al. 2000). Furthermore, PI3K γ has also 25 been implicated in thrombolytic diseases (e.g., thromboembolism, ischemic diseases, heart attacks, and stroke) (Hirsch et al. *FASEB J.* 2000;15(11):2019-2021; and Hirsch et al. *FASEB J.*, July 9 2001;10.1096/fj.00-0810fje (cited herein as Hirsch et al., 2001).

30 Inhibitors of members of the PI3Ks are being developed for the treatment of human disease (see e.g., WO 01/81346; WO 01/53266; and WO 01/83456).

Therefore, there is a need in the art for compounds that can inhibit PI3Ks for use as pharmaceutical agents.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides for compounds of formula I:



or a pharmaceutically acceptable salt thereof; wherein W is selected from the group consisting of: O, S, and NR²¹; wherein R²¹ is selected from the group consisting of: -H, -CH₃, a C₁₋₆alkyl, and phenyl; wherein Q is (CR²R³)_n, wherein R² and R³ are independently selected from H or -CH₃, wherein n is 0 or 1; wherein E is (CR⁴R⁵)_p, wherein R⁴ and R⁵ are independently selected from H or -CH₃; wherein p is 0 or 1; wherein D is O or S; wherein R⁶ is selected from the group consisting of H, a C₁₋₉alkyl, a -CO-C₁₋₉alkyl, a C₃₋₈cycloalkyl, a -C(O)-C₁₋₃alkylene-C₃₋₈cycloalkyl, a (C₁₋₆alkyl)-C₃₋₈cycloalkyl, a -O-CH₂-C₃₋₈cycloalkyl, a group of formula -A-B-L, and a group of formula -X-V-U-T; wherein A is absent, or -O-, wherein B is a C₁₋₆alkylene, wherein L is -OR²⁴, -C(O)R²⁴, -OC(O)R²⁴, -C(O)OR²⁴, -SO₂-R²⁴, -NHC(O)R²⁴, -NR²⁴R²⁶, -C(O)NR²⁴R²⁶, -OC(O)NR²⁴R²⁶, -NC(O)OR²⁴, a 3- to 8-membered heterocycloalkyl, a 6- to 11-membered bicyclic heterocycloalkyl, a 6- to 9-membered bridged bicyclic heterocycloalkyl, a 5-membered heteroaryl, a 6-membered heteroaryl, an 8- to 12-membered bicyclic heteroaryl, a phenyl, a naphthalenyl or a 9- to 12-membered bicyclic aryl; wherein R²⁴ and R²⁶ are

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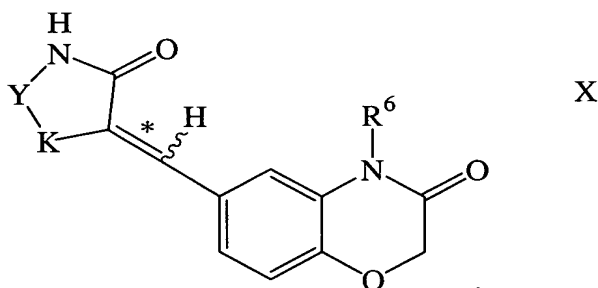
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independently selected from the group consisting of: a C₁₋₆alkyl, phenyl, naphthalenyl or a 9- to 12-membered bicyclic aryl, a 5-membered heteroaryl, a 6-membered heteroaryl, an 8- to 12-membered bicyclic heteroaryl, a C₁₋₆alkylene-phenyl, C₁₋₆alkylene-naphthalenyl or a C₁₋₆alkylene-(9- to 12-membered bicyclic aryl), a C₁₋₆alkylene-(5-membered heteroaryl), C₁₋₆alkylene-(6-membered heteroaryl), a C₁₋₆alkylene-(8- to 12-membered bicyclic heteroaryl), C₁₋₆alkylene-(3- to 8-membered heterocycloalkyl), C₁₋₆alkylene-(6- to 11-membered bicyclic heterocycloalkyl), C₁₋₆alkylene-(6- to 9-membered bridged bicyclic heterocycloalkyl), and H, wherein X is C₁₋₃alkylene, -O-C₁₋₃alkylene, -C₁₋₃alkylene-CO-, -C₁₋₃alkylene-C(O)O-, -C₁₋₃alkylene-C(O)-CH₂-, -C₁₋₃alkylene-O-, -C₁₋₃alkylene-S(O)-, -C₁₋₃alkylene-S-, or -C₁₋₃alkylene-SO₂-; wherein V is a 9- to 12-membered bicyclic arylene, a naphthalenylene, a phenylene, a 5-membered heteroarylene, a 6-membered heteroarylene, an 8- to 12-membered bicyclic heteroarylene, a 3- to 8-membered heterocycloalkylene, a 6- to 11-membered bicyclic heterocycloalkylene, or a 6- to 9-membered bridged bicyclic heterocycloalkylene; wherein U is -CO-, -O-, -CH₂O-, a C₁₋₃alkenylene, -(CH₂)_m-, -O-CH₂-, NH-, or is absent, wherein m is an integer from 1 to 3; wherein T is a C₃₋₈cycloalkyl, a 9- to 12-membered bicyclic aryl, a naphthalenyl, a phenyl, a 5-membered heteroarylene, a 6-membered heteroarylene, an 8- to 12-membered bicyclic heteroarylene, a piperizinyl, a pyridinyl, a 3- to 8-membered heterocycloalkyl, a 6- to 11-membered bicyclic heterocycloalkyl, a 6- to 9-membered bridged bicyclic heterocycloalkyl, a piperidinyl, a morpholinyl, or an aza-spiro[5.5]undecyl; wherein R⁷ is H, F, CF₃, or CH₃; wherein R⁸ is H, -CH₂COOH, phenyl, -CH₃, a C₁₋₆alkyl, or a C₂₋₆alkenyl; wherein Y is C(O), or C(S); wherein K is NH, O, CH₂, or S; wherein G is N or C; wherein R⁹ is H, F, CF₃, or CH₃; wherein R¹⁰ is H, -O-C₁₋₃alkyl, a C₁₋₃alkyl, NO₂, NR¹⁶R¹⁸, a S-C₁₋₃alkyl, F or Cl, wherein if G is N, then R¹⁰ is absent, wherein R¹⁶ and R¹⁸ are independently selected from the group consisting of: H and C₁₋₃alkyl; wherein R¹² is H, or C₁₋₃alkyl; and

wherein the stereochemistry of the double bond denoted “*” is entgegen or zusammen. In yet other embodiments, X is a C₁₋₃alkylene, and V is a phenylene, naphthalenylene, or a 9- to 12-membered bicyclic arylene. In other embodiments, X is a C₁₋₃ alkylene, and V is a 5-membered heteroarylene, a 6-membered heteroarylene, or an 8- to 12-membered bicyclic heteroarylene. In still other embodiments, A is absent, B is a C₁₋₃alkylene, L is a 5-membered heteroaryl, a 6-membered heteroaryl, an 8- to 12-membered bicyclic heteroaryl, a phenyl, a naphthalenyl or a 9- to 12-membered bicyclic aryl.

In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, and R², R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula X:



In certain embodiments, R⁶ is –A-B-L or –X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula X include, but are not limited to:

- 4-(4-tert-Butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;
- 5-[4-(2,6-Di-tert-butyl-pyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione;
- 6-(Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-(4-trifluoromethyl-phenyl)-ethyl]-4H-benzo[1,4]oxazin-3-one;
- 4-(4-Methanesulfonyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;
- 4-(3-tert-Butyl-5-hydroxymethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;
- 5-[4-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione;

5-{4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene}-thiazolidine-2,4-dione;

4-Cyclohexylmethyl-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

5 4-[3-*tert*-Butyl-5-(morpholine-4-carbonyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

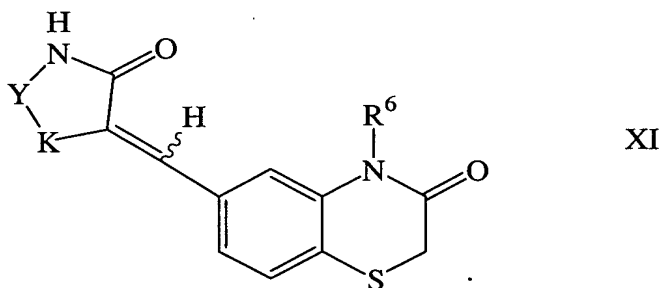
5-[1-[4-(3-*tert*-Butyl-5-morpholin-4-ylmethyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione;

10 4-(3,5-Difluoro-4-hydroxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

5-[4-(3-Chloro-4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione; and

15 4-(1-*tert*-Butyl-5-methyl-1H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.

In certain embodiments, W is S, D is O, G is C, n is 1, p is 0, and R², R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula XI:

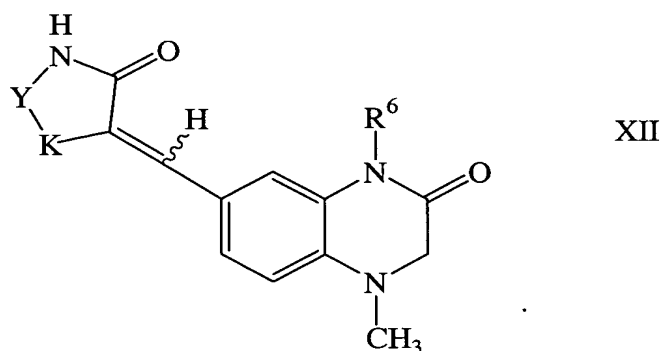


20 In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XI include, but are not limited to:

4-Benzyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one; and

25 4-(3,5-Di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one.

In certain embodiments, W is N, R²¹ is methyl, D is O, G is C, n is 1, p is 0, and R², R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula XII:

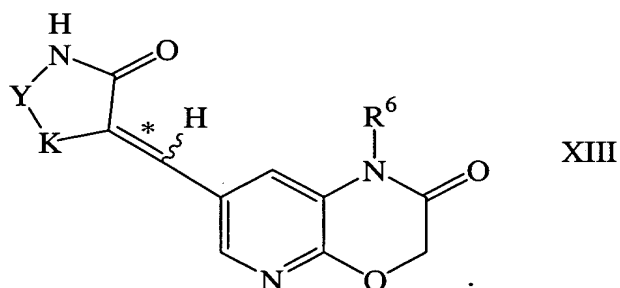


In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XII include, but are not limited to:

4-Methyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-3,4-dihydro-1H-quinoxalin-2-one; and

1-Benzyl-4-methyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-3,4-dihydro-1H-quinoxalin-2-one.

In certain embodiments, W is O, D is O, G is N, n is 1, p is 0, and R², R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula XIII:

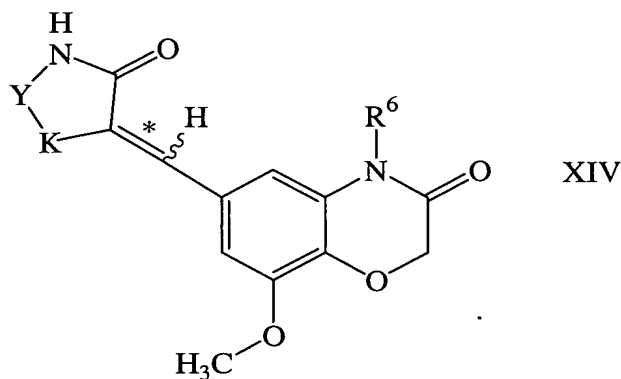


In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XIII include, but are not limited to:

1-Benzyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-1H-pyrido[2,3-b][1,4]oxazin-2-one; and

7-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-1H-pyrido[2,3-b][1,4]oxazin-2-one.

In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R¹⁰ is methoxy, and R², R³, R⁷, R⁸, R⁹, and R¹² are H—a compound of Formula XIV:

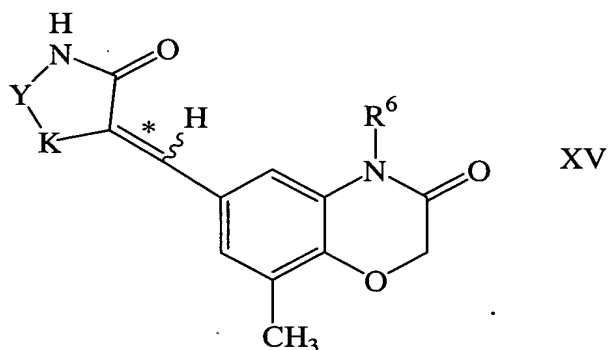


In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XIV include, but are not limited to:

8-Methoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; and

4-(3,5-Di-*tert*-butyl-benzyl)-8-methoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.

In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R¹⁰ is methyl, and R², R³, R⁷, R⁸, R⁹, and R¹² are H—a compound of Formula XV:

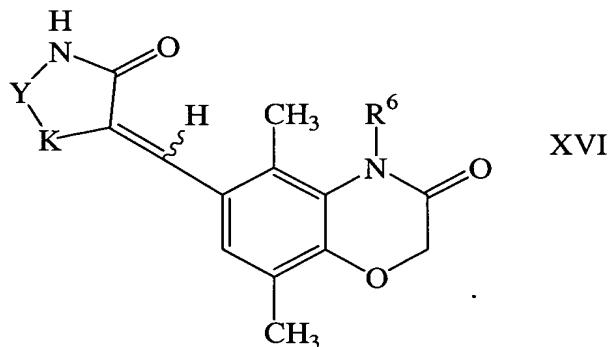


In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted

cyclohexyl. Examples of compounds of Formula XV include, but are not limited to:

4-(3,5-Dimethyl-benzyl)-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; and

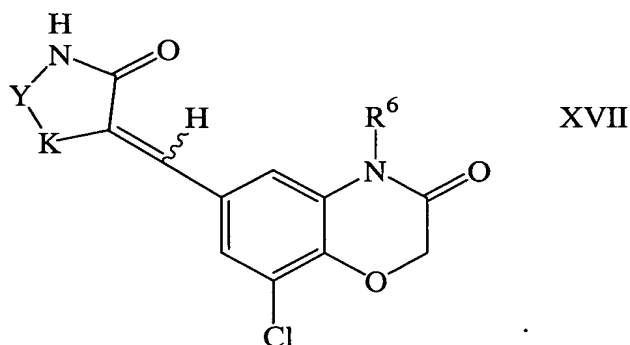
5 In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R⁷ and R¹⁰ are methyl, and R², R³, R⁸, R⁹, and R¹² are H—a compound of Formula XVI:



10 In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XVI include, but are not limited to:

5,8-Dimethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.

15 In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R¹⁰ is chloro, and R², R³, R⁷, R⁸, R⁹, and R¹² are H—a compound of Formula XVII:



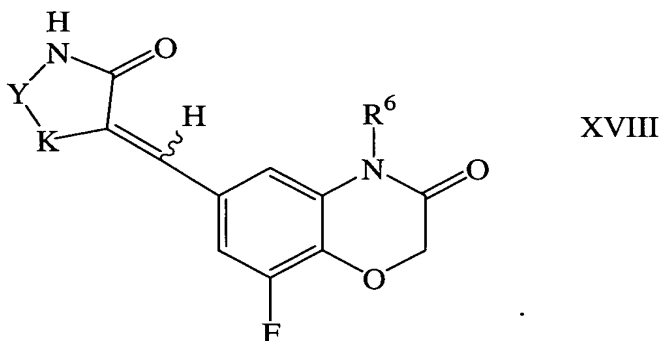
In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted

cyclohexyl. Examples of compounds of Formula XVII include, but are not limited to:

8-Chloro-4-(3,5-di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; and

5 8-Chloro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.

In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R¹⁰ is fluoro, and R², R³, R⁷, R⁸, R⁹, and R¹² are H—a compound of Formula XVIII:



10 In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XVIII include, but are not limited to:

15 5-[1-{4-[3-*tert*-Butyl-5-(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-meth-(Z)-ylidene]-thiazolidine-2,4-dione;

8-Fluoro-4-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

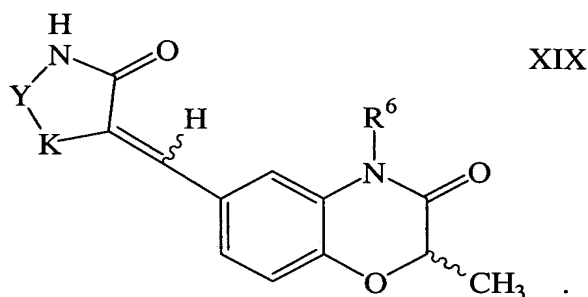
20 5-[8-Fluoro-4-(4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione;

4-(3-Chloro-4-fluoro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinolin-6-ylmethyl-4H-1,4-benzoxazin-3-one; and

25 4-(3,4-Dichloro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.

In certain embodiments, W is O, D is O, G is C, n is 1, p is 0, R² is methyl, and R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula XIX:

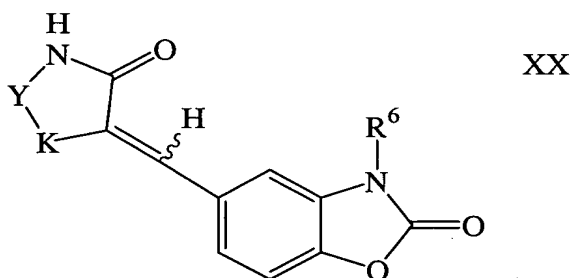


In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XIX include, but are not limited to:

(S)-2-Methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; and

(S)-4-Benzyl-2-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.

In certain embodiments, W is O, D is O, G is C, n is 0, p is 0, and R², R³, R⁷, R⁸, R⁹, R¹⁰, and R¹² are H—a compound of Formula XX:



In certain embodiments, R⁶ is -A-B-L or -X-V-U-T, where L and V are phenyl or a substituted phenyl. In other embodiments, R⁶ is cyclohexyl or substituted cyclohexyl. Examples of compounds of Formula XX include, but are not limited to:

3-(3,4-Dichloro-benzyl)-5-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-3H-benzooxazol-2-one; and

3-Benzyl-5-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-3H-benzooxazol-2-one.

In another aspect, the invention provides for pharmaceutical compositions that comprise a therapeutically effective amount of a compound of Formula I; and a pharmaceutically acceptable carrier. In certain embodiments, these compositions are useful in the treatment of a PI3K-mediated disorder or condition.

5 The compounds of the invention can also be combined in a pharmaceutical composition that also comprise compounds that are useful for the treatment of cancer, a thrombolytic disease, heart disease, stroke, an inflammatory disease such as rheumatoid arthritis, or another PI3K-mediated disorder.

In another aspect, the present invention provides for methods of treating a

10 subject suffering from a PI3K-mediated disorder or condition comprising: administering, to a subject suffering from a PI3K-mediated condition or disorder, a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier. In certain embodiments, the PI3K-mediated condition or disorder is selected from the group

15 consisting of: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, inflammatory diseases, and autoimmune diseases. In other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary

20 embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease. In still other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: cancer, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, and leukemia. In yet another

25 embodiment, the PI3K-mediated condition or disorder is selected from the group consisting of: type II diabetes. In still other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease. In certain embodiments, the subject is a human.

30 DEFINITIONS

As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

A “PI3K-mediated disorder or condition” is characterized by the participation of one or more PI3Ks or a PI3P phosphatase, (e.g., PTEN, etc.) in the inception, manifestation of one or more symptoms or disease markers, severity, or progression of a disorder or condition. PI3K-mediated disorders and conditions include, but are not limited to: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, inflammatory diseases, pulmonary fibrosis, autoimmune diseases, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, coronary artery disease, cancer, breast cancer, glioblastoma, endometrial carcinoma, hepatocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, lymphoproliferative disorders, type II diabetes, respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease.

A PI3K is an enzyme that is able to phosphorylate the 3'-OH of a phosphoinositol to generate PI3P. PI3Ks include, but are not limited to, PI3K α , PI3K β , PI3K γ , and PI3K δ . A PI3K typically comprises at least one catalytic subunit (e.g., p110 γ), and may further comprise a regulatory subunit (e.g., p101, etc.).

The term “alkyl group” or “alkyl” includes straight and branched carbon chain radicals. For example, a “C₁₋₆ alkyl” is an alkyl group having from 1 to 6 carbon atoms. Examples of straight-chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, etc. Examples of branched-chain alkyl groups include, but are not limited to, isopropyl, *tert*-butyl, isobutyl, etc.

Moreover, the term alkyl includes both “unsubstituted alkyls” and “substituted alkyls,” the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons (e.g., replacing a hydrogen on 1, 2, 3, 4, 5, or 6 carbons) of the hydrocarbon backbone. Such substituents can include, but are not limited to, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halo, I, Br, Cl, F, -OH, -

COOH, sulfhydryl, (C₁-C₆-alkyl)S-, C₁-C₆-alkylsulfinyl, nitro, cyano, trifluoromethyl, -NH₂, =O, =S, =N-CN, =N-OH, -OCH₂F, -OCHF₂, -OCF₃, -SCF₃, -SO₂-NH₂, C₁-C₆-alkoxy, -C(O)O-(C₁-C₆ alkyl), -O-C(O)-(C₁-C₆ alkyl), -C(O)-NH₂, -C(O)-N(H)-C₁-C₆ alkyl, -C(O)-N(C₁-C₆ alkyl)₂ -OC(O)-NH₂, -C(O)-H, -C(O)-(C₁-C₆ alkyl), -C(S)-(C₁-C₆ alkyl), -NR⁷⁰R⁷², where R⁷⁰ and R⁷² are each independently selected from H, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, and C(O)-C₁-C₆-alkyl.

Alkyl substituents may also include heterocycloalkyl, heteroaryl, and aryl substituents such as, a (C₃-C₈)cycloalkyl, a 3- to 8-membered heterocycloalkyl, phenyl, naphthalenyl, benzyl, phenoxy, naphthalenyl-O-, a 9- to 12-membered bicyclic aryl, a 5-membered heteroaryl, 6-membered heteroaryl, and a 8- to 12-membered bicyclic heteroaryl.

Typical substituted alkyl groups thus are aminomethyl, 2-nitroethyl, 4-cyanobutyl, 2,3-dichloropentyl, and 3-hydroxy-5-carboxyhexyl, 2-aminoethyl, pentachloroethyl, trifluoromethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, methanysulfanylmethyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, and pentafluoroethyl.

“Alkoxy” refers to the alkyl groups mentioned above bound through oxygen, examples of which include methoxy, ethoxy, isopropoxy, *tert*-butoxy, and the like. In addition, alkoxy refers to polyethers such as O-(CH₂)₂-O-CH₃, and the like. The term “alkoxy” is intended to include both substituted and unsubstituted alkoxy groups. Alkoxy groups can be substituted on carbon atoms with groups such as those set out above for alkyl. Typical substituted alkoxy groups include aminomethoxy, trifluoromethoxy, 2-diethylaminoethoxy, 2-ethoxycarbonylethoxy, 3-hydroxypropoxy, and the like.

“Alkanoyl” groups are alkyl linked through a carbonyl, e.g., C₁-C₆alkyl-C(O)-. Such groups include formyl, acetyl, propionyl, butyryl, and isobutyryl. The term “alkanoyl” is intended to include both substituted and unsubstituted alkanoyl groups. Alkanoyl groups can be substituted with groups such as those set out above for alkyl.

“Acyl” means an alkyl or aryl (Ar) group bonded through a carbonyl group, i.e., R-C(O)-. For example, acyl includes a C₁-C₆ alkanoyl, including substituted alkanoyl. The term “acyl” is intended to include both substituted and unsubstituted acyl groups. Acyl groups can be substituted with groups such as those set out above for alkyl.

“Halo” includes fluoro, chloro, bromo, and iodo.

“Alkenyl” means straight and branched hydrocarbon radicals having 2 or more carbon atoms and comprising at least one double bond and includes ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like. The term “alkenyl” is intended to include both substituted and unsubstituted alkenyl groups. A “C₂-C₆-alkenyl” is an alkenyl group having from 2 to 6 carbon atoms. Alkenyl groups can be substituted with groups such as those set out above for alkyl.

“Alkynyl” means straight and branched hydrocarbon radicals having 2 or more carbon atoms and comprising at least one triple bond and includes ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like. The term “alkynyl” is intended to include both substituted and unsubstituted alkynyl groups. Alkynyl groups can be substituted with groups such as those set out above for alkyl. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term C₂-C₆ includes alkynyl groups containing 2 to 6 carbon atoms.

“Carbocycle” or “Cycloalkyl” means a mono or bicyclic carbocyclic ring functional group including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl; wherein the cycloalkyl group may optionally contain 1 or 2 double bonds (i.e., a cycloalkylenyl) including, but not limited to, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term “cycloalkyl” is intended to include both substituted and unsubstituted cycloalkyl groups. Cycloalkyl groups and cyclohexyl groups can be substituted with groups such as those set out above for alkyl. Unless otherwise indicated, the term “(C₃-C₈)cycloalkyl” refers to a cycloalkyl group containing from 3 to 8 carbons. Thus, the term “(C₃-C₈)cycloalkyl” encompasses a

monocyclic cycloalkyl group containing from 3 to 8 carbons and a bicyclic cycloalkyl group containing from 6 to 8 carbons.

The phrase "3- to 8-membered heterocycloalkyl" means a stable cyclic group having carbon atoms and 1 to 3 heteroatoms independently selected from S, N or O, wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, respectively. Optionally, a 3- to 8-membered heterocycloalkyl may contain 1 or 2 carbon-carbon or carbon-nitrogen double bonds. Illustrative examples of 3- to 8-membered heterocycloalkyl include aziridin-1-yl, 1-oxa-cyclobutan-2-yl, tetrahydrofuran-3-yl, morpholin-4-yl, 2-thiacyclohex-1-yl, 2-oxo-2-thiacyclohex-1-yl, 2,2-dioxo-2-thiacyclohex-1-yl, and 4-methyl-piperazin-2-yl.

The term "heterocycloalkyl" is intended to include both substituted and unsubstituted heterocycloalkyl groups. Heterocycloalkyl groups can be substituted with 1 to 4 groups such as those set out above for alkyl. Illustrative examples of substituted 3- to 8-membered heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, and 1-cyclopropyl-4-methyl-piperazin-2-yl.

Unless otherwise indicated, the foregoing heterocycloalkyls can be C-attached or N-attached where such is possible and which results in the creation of a stable structure. For example, piperidinyl can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached).

Embraced within the term "heterocycloalkyl" are 5 membered rings having one carbon-carbon or one carbon-nitrogen double bond in the ring (e.g., 2-pyrrolinyl, 3-pyrrolinyl, etc.) and 6 membered rings having one carbon-carbon or one carbon-nitrogen double bond in the ring (e.g., dihydro-2H-pyranyl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, etc.).

A "3-membered heterocycloalkyl" is a stable 3-membered, monocyclic cycloalkyl ring having 2 carbon atoms and 1 heteroatom selected from the group consisting of: 1 O; 1 S; and 1 N. Illustrative examples of stable 3-membered heterocycloalkyls include oxiranyl, aziridinyl, and thiiranyl.

A "4-membered heterocycloalkyl" is a stable 4-membered, monocyclic cycloalkyl ring having 3 carbon atoms and 1 heteroatom selected from the group

consisting of: 1 O; 1 S; and 1 N. Illustrative examples of stable 4-membered heterocycloalkyls include oxetanyl, azetidiny, and thietanyl.

A "5-membered heterocycloalkyl" is a stable 5-membered, monocyclic cycloalkyl ring having from 1 to 4 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 1 S; 1 N; 2 N; 3 N; 1 S and 1 N; 1 S, and 2 N; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 5-membered heterocycloalkyls include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, imidazolidinyl, oxazolidinyl, imidazolinyl, isoxazolidinyl, pyrrolidinyl, 2-pyrrolinyl, and 3-pyrrolinyl.

A "6-membered heterocycloalkyl" is a stable 6-membered, monocyclic cycloalkyl ring having from 3 to 5 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 3 O; 1 S; 2 S; 3 S; 1 N; 2 N; 3 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 6-membered heterocycloalkyls include tetrahydropyranyl, dihydropyranyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydropyrimidine, morpholinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl, and trithianyl.

A "7-membered heterocycloalkyl" is a stable 7-membered, monocyclic cycloalkyl ring having from 5 or 6 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 1 S; 2 S; 1 N; 2 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 7-membered heterocycloalkyls include azepanyl, 2,3,4,5-tetrahydro-1H-azepinyl, oxepanyl, 2,3,4,5-tetrahydro-1H-oxepinyl, thiepanyl, and 2,3,4,5-tetrahydro-1H-thiepinyl.

An "8-membered heterocycloalkyl" is a stable 8-membered, monocyclic cycloalkyl ring having from 5 to 7 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 3 O; 1 S; 2 S; 3 S; 1 N; 2 N; 3 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 8-membered heterocycloalkyls include azocanyl, thiocanyl, oxocanyl, 3,4,5,6-tetrahydro-2H-oxocinyl, etc.

The term “3- to 8-membered heterocycloalkyl” includes saturated and unsaturated “3- to 8-membered heterocycloalkyls.” “3- to 8-membered heterocycloalkyls” may be substituted as set out above for alkyl.

5 The term “6- to 11-membered bicyclic heterocycloalkyl” refers to a stable ring structure which is either saturated or unsaturated, and which is the result of the fusion of a 5-, 6-, or 7-membered heterocycloalkyl to a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl; or a 5-, 6-, or 7-membered heterocycloalkyl to a C₃₋₇-cycloalkyl, wherein the fusion junctions are at adjacent ring atoms. The term “6- to 11-membered bicyclic heterocycloalkyl” includes saturated and
10 unsaturated “6- to 11-membered bicyclic heterocycloalkyls.” “6- to 11-membered bicyclic heterocycloalkyls” may be substituted as set out above for alkyl. Examples of “6- to 11-membered bicyclic heterocycloalkyls” include 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[4.1.0]-heptanyl.

15 The term “6- to 9-membered bridged bicyclic heterocycloalkyl” refers to a stable ring structure which is either saturated or unsaturated, and which is the result of the fusion of 5-, 6-, or 7-membered heterocycloalkyl to a 3-, 4-, or 5-membered heterocycloalkyl; or a 5-, 6-, or 7-membered heterocycloalkyl to a C₅₋₇-cycloalkyl, wherein the fusion junctions have 1 to 3 intervening ring atoms. The term “6- to 9-membered bridged bicyclic heterocycloalkyl” includes saturated
20 and unsaturated “6- to 9-membered bridged bicyclic heterocycloalkyls.” “6- to 9-membered bridged bicyclic heterocycloalkyls” may be substituted as set out above for alkyl. Examples of “6- to 9-membered bridged bicyclic heterocycloalkyls” include 3-azabicyclo[4.2.1]nonanyl and 7-azabicyclo[2.2.1]heptanyl.

25 An aryl group is an aromatic hydrocarbon radical. Furthermore, the term “aryl” includes multicyclic aryl groups, bicyclic, e.g., naphthyl. Typical aryl groups include phenyl, and naphthyl. Typical substituted aryl groups include 3-chlorophenyl, 2,6-dibromophenyl, 2,4,6-tribromophenyl, 4,7-dichloronaphthyl, 2,6-dichlorophenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 3-amino-
30 4-nitrophenyl, 3,5-dihydroxyphenyl, and the like. Unless otherwise indicated, a C₆-aryl is a phenyl group. Phenyl may be unsubstituted or substituted at one or more positions with a substituent such as, but not limited to, those substituents

described above for alkyl. Naphthalenyl may be unsubstituted or substituted at one or more positions with a substituent such as, but not limited to, those substituents described above for alkyl. The term "aryl" is intended to include both substituted and unsubstituted phenyl groups. An aryl or C₆- or C₁₀-aryl can be optionally substituted on any ring carbon atom by 1 to 4 functional groups per ring, wherein the substituents are set out above for alkyl.

A "9- to 12-membered bicyclic aryl" is a stable ring structure formed by the fusion of a benzene ring to:

- (1) a C₅₋₈ monocyclic cycloalkyl (e.g., indanyl; 1,2,3,4-tetrahydro-naphthalenyl; 6,7,8,9-tetrahydro-5H-benzocycloheptenyl, etc.);
- (2) a 5- to 7-membered heterocycloalkyl (e.g., benzoxazine, benzthiazine, chromanyl, 1,2,3,4-tetrahydro-quinolinyl, etc.); or
- (3) another benzene ring (e.g., naphthalenyl);

wherein the fusion junctions are at adjacent carbons on the benzene ring.

A "5-membered heteroaryl" is a stable 5-membered, monocyclic, aromatic ring radical having from 1 to 4 carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of: 1 O; 1 S; 1 N; 2 N; 3 N; 4 N; 1 S and 1 N; 1 S and 2 N; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of stable 5-membered heteroaryls include, but are not limited to, furanyl, 2-furanyl, 3-furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, 2-, 3-, or 4-pyridinyl, pyrimidinyl, 2-, 4-, or 5-pyrimidinyl, pyrazolyl, pyrrolyl, 2- or 3-pyrrolyl, pyrazinyl, pyridazinyl, 3- or 4-pyridazinyl, 2-pyrazinyl, thienyl, 2-thienyl, 3-thienyl, tetrazolyl, thiazolyl, thiadiazolyl, triazinyl and triazolyl.

A "6-membered heteroaryl" is a stable 6-membered, monocyclic, aromatic ring radical having from 3 to 5 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 N; 2 N; and 3 N. Illustrative examples of stable 6-membered heteroaryl include pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyridazin-4-yl, and pyrazin-2-yl.

An "8- to 12-membered bicyclic heteroaryl" is a stable ring structure formed by the fusion of 5- or 6-membered heteroaryl to:

- (1) an independently selected 5-membered heteroaryl;

- (2) an independently selected 6-membered heteroaryl (e.g., naphthyridinyl, pteridinyl, phthalazinyl, purinyl, etc.);
- (3) a C₅₋₈ monocyclic cycloalkyl;
- (4) a 5- to 7-membered heterocycloalkyl; or
- 5 (5) a benzene ring (e.g., benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, cinnolinyl, furopyridinyl, indolinyl, indolizinyl, indolyl, or 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 3H-indolyl, quinazolinyl, quinoxalinyl, isoindolyl, and isoquinolinyl), wherein the
10 fusion junctions are at adjacent ring atoms. The fusion junctions may be at nitrogen (e.g., indolizine) or carbon atoms in the 5- or 6-membered heteroaryl.

A heteroaryl can also include ring systems substituted on ring carbons with one or more –OH functional groups (which may further tautomerize to give a ring
15 C=O group) and or substituted on a ring sulfur atom by 1 or 2 oxygen atoms to give S=O, or SO₂ groups, respectively.

The phrase “pharmaceutical composition” refers to a composition suitable for administration in medical or veterinary use.

The phrase “therapeutically effective amount” means an amount of a
20 compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit, halt, or cause an improvement in the disorder or condition being treated in a particular subject or subject population. For example in a human or other mammal, a therapeutically effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United
25 States Food and Drug Administration, or equivalent foreign agency, for the particular disease and subject being treated.

It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

30 Some of the compounds in the present invention may exist as stereoisomers, including enantiomers, diastereomers, and geometric isomers. Geometric isomers include compounds of the present invention that have alkenyl

groups, which may exist as *entgegen* or *zusammen* conformations, in which case all geometric forms thereof, both *entgegen* and *zusammen*, *cis* and *trans*, and mixtures thereof, are within the scope of the present invention. Some compounds of the present invention have cycloalkyl groups, which may be substituted at more than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention. All of these forms, including (R), (S), epimers, diastereomers, *cis*, *trans*, *syn*, *anti*, (E), (Z), tautomers, and mixtures thereof, are contemplated in the compounds of the present invention.

The compounds to be used in the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

The compounds of the present invention (e.g., compounds of Formula I) are capable of further forming both pharmaceutically acceptable salts, including but not limited to acid addition and/or base salts. This invention also provides pharmaceutical compositions comprising a compound of Formula I together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. All of these forms can be used in the method of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorus, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are the salts of amino acids

such as arginate, gluconate, galacturonate, and the like; see, for example, Berge et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977;66:1-19.

The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metal hydroxides, or of organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine (ethane-1,2-diamine), N-methylglucamine, and procaine; see, for example, Berge et al., supra., 1977.

The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in a conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

"Cancer cells," "transformed" cells, or "transformation" in tissue culture, refers to spontaneous or induced phenotypic changes that do not necessarily involve the uptake of new genetic material. Although transformation can arise from infection with a transforming virus and incorporation of new genomic DNA, or uptake of exogenous DNA, it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation is associated with phenotypic changes, such as immortalization of cells, aberrant growth control, and/or malignancy (see, Freshney, *Culture of Animal Cells: A Manual of Basic Technique*, 4th ed. Wiley-Liss, Inc., 2000).

The term “subject” refers to a member of the class Mammalia. Examples of mammals include, without limitation, humans, primates, chimpanzees, rodents, mice, rats, rabbits, horses, livestock, dogs, cats, sheep, and cows.

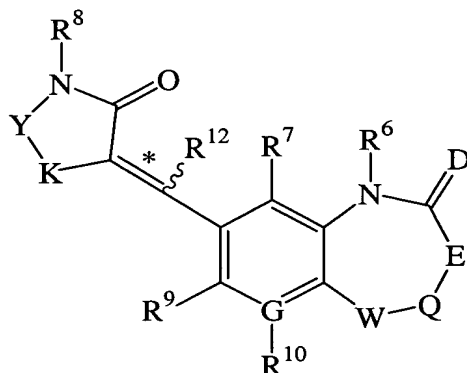
The term “treatment” includes the acute or prophylactic diminishment or
5 alleviation of at least one symptom or characteristic associated or caused by the
disorder being treated. For example, treatment can include diminishment of
several symptoms of a disorder or complete eradication of a disorder.

The term “administering” refers to the method of contacting a compound with a subject. Modes of “administering” may include but are not limited to, methods that involve contacting the compound intravenously, intraperitoneally, intranasally, transdermally, topically, via implantation, subcutaneously, parentally, intramuscularly, orally, systemically, and via adsorption.

DETAILED DESCRIPTION OF THE INVENTION

I. INTRODUCTION

15 The present invention relates to compounds of Formula I and pharmaceutically acceptable salts thereof:



I

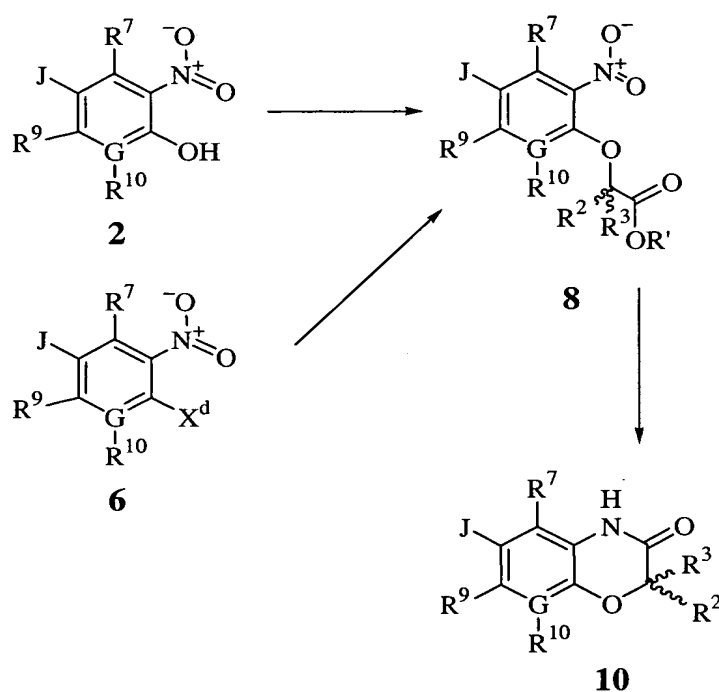
wherein W, Q, E, D, R⁶, R⁷, R⁸, Y, K, R⁹, R¹⁰, R¹², G, and the double bond denoted “*” have any of the values defined in the specification. Compounds of Formula I, and pharmaceutical compositions thereof, are useful as agents in the treatment of diseases and conditions, including inflammatory diseases, cardiovascular diseases, and cancers. Also disclosed are pharmaceutical compositions comprising one or more compounds of Formula I, processes for preparing compounds of Formula I, and intermediates useful for preparing

compounds of Formula I. In particular, compounds of the present invention are useful for the treatment of a PI3K-mediated disorder or condition.

II. PREPARATION OF COMPOUNDS

Compounds of the present invention (e.g., compounds of Formula I) can be prepared by applying synthetic methodology known in the art and synthetic methodology outlined in the schemes set forth below.

Scheme 1

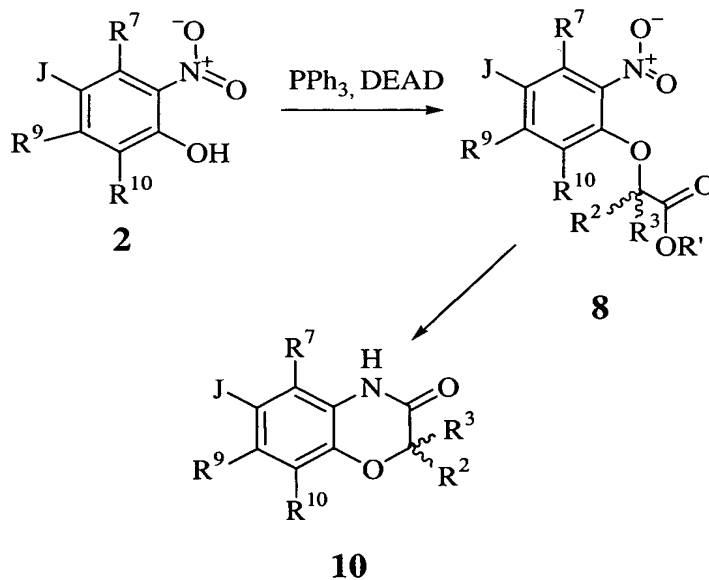


In Scheme 1, 2 is reacted with a compound 3 R'-O-C(O)-C(R²R³)-X^e (e.g., ethyl bromoacetate (Br-CH₂-C(O)O-CH₂CH₃), in THF with a non-nucleophilic base, e.g., a hydride such as NaH, to give 8. 2 is an appropriately substituted alpha nitrobenzene (e.g., 4-hydroxy-3-nitrobenzaldehyde) or nitropyridine. R' of 3 is typically a C₁-C₆alkyl (e.g., CH₃, CH₂CH₃, t-butyl, etc.). X^e of 3 represents Cl, I, or Br. Unless otherwise noted, group denoted "J" on 2 can be Br, -CHO, -CH₂OH, -C(O)CH₃, -C(O)C₁-C₆alkyl, -C(O)R¹²- or -CH₃. The groups denoted R², R³, R¹⁰, R¹², and Q are as defined herein. A wavy bond denotes undefined stereochemistry, e.g., R or S; E (entgegen) or Z

(zusammen); etc., depending on the context. The nitro moiety of **8** is then treated with a reducing agent such as iron(II)sulfate, zinc metal in acid, tin metal in acid, tin(II)chloride, dithionate; or catalytically with hydrogen gas and a catalyst (e.g., Raney Nickel) to give an amine which cyclizes in situ immediately or upon heating to yield **10**.

Alternatively, an appropriately substituted alpha nitrobenzene or nitropyridine **6** (e.g., 5-bromo-2-chloro-3-nitropyridine) can be reacted with **5** ($R'-O-C(O)-C(R^2R^3)-R''$) in THF with a non-nucleophilic base, e.g., a hydride such as NaH, to yield **8**. X^d of **3** represents Cl, I, or Br. R' of **5** is typically a C_1-C_6 alkyl (e.g., CH_3 , CH_2CH_3 , t-butyl, etc.). R'' of **5** is OH or SH. Examples of **5** include, but are not limited to, methylglycolate, methyl(R)-(+)-lactate, and hydroxy-acetic acid ethyl ester. A nitropyridine **6** can be provided by reacting an appropriately substituted pyridinol (e.g., 5-bromo-3-nitro-2-pyridinol) in DMF with phosphorus oxychloride.

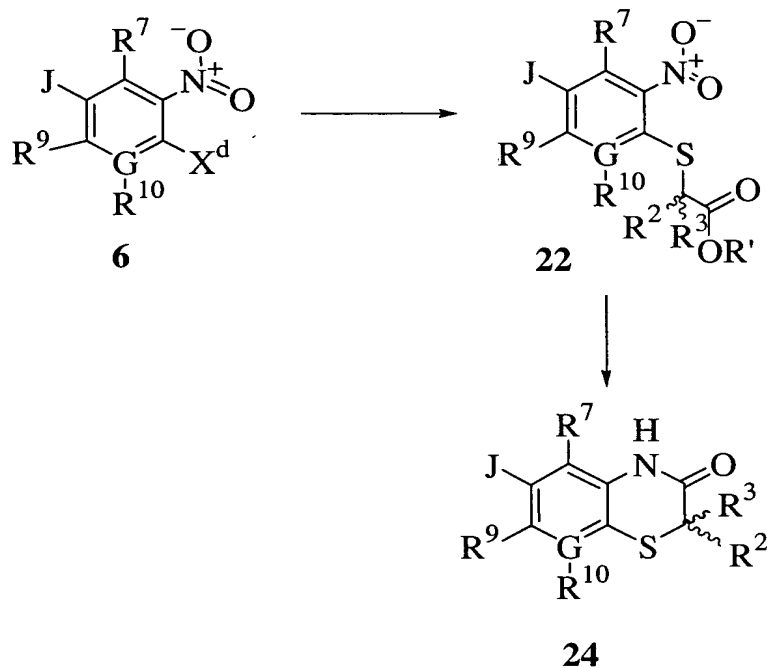
Scheme 1b



Alternatively, **2** can be reacted with **5** as in Scheme 1b under Mitsunobu conditions (e.g., PPh_3 (triphenylphosphine) and DEAD (diethyl azodicarboxylate)) to arrive at **8**. The reaction can be carried out with or without the addition of an

organic base or inorganic base (e.g., Na_2CO_3 , K_2CO_3 , NaH , CsCO_3 , etc.) in a solvent such as ethanol, acetonitrile, or DMF (dimethylformamide).

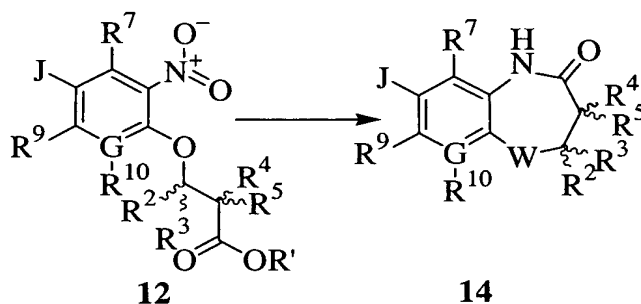
Scheme 2



5 In Scheme 2, compounds of formula 22 can be generated. An appropriately substituted alpha nitrobenzene or nitropyridine 6 (e.g., 4-chloro-3-nitrobenzaldehyde) can be reacted with 21 (HS-C(R²R³)-COOH) (e.g., thioglycolic acid; HS-CH₂-COOH) triethylamine and in acetonitrile to yield 22 (e.g., 4-formyl-2-nitro-phenylsulfanyl)-acetic acid). 22 in ammonium hydroxide is then treated with iron (II) sulfate heptahydrate in water and heated to 90°C for 1 hour. The iron salts are filtered away, and the filtrate is acidified (e.g., with 6N HCl). The resulting precipitate is then refluxed in ethanol and cooled to provide 24 (e.g., 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxaldehyde).

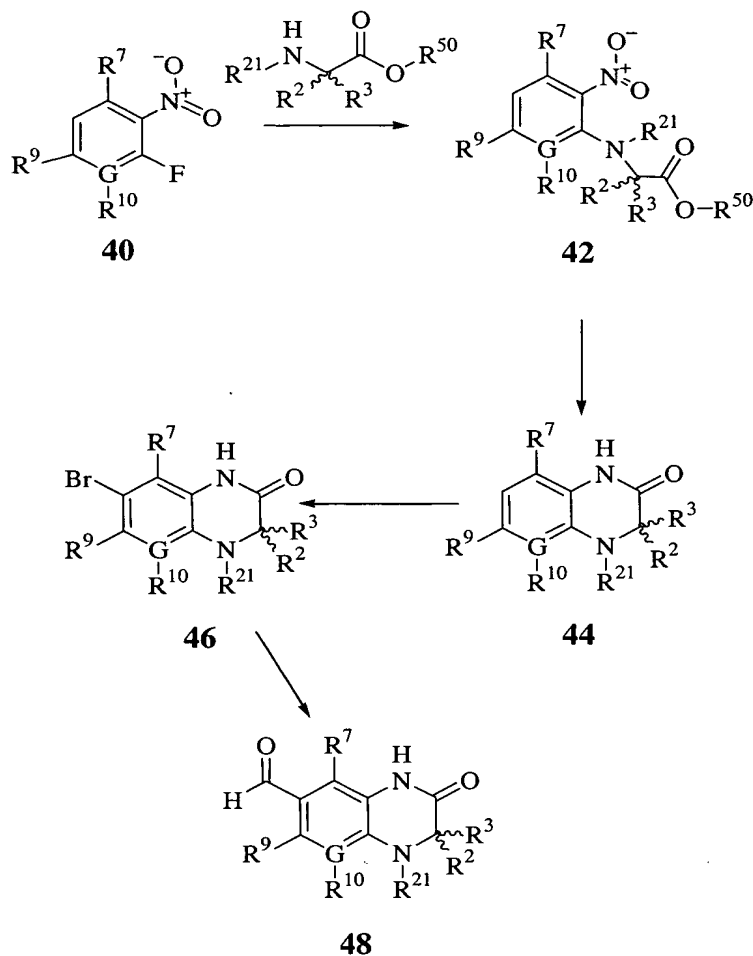
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Scheme 3



The compounds of formula **12** can be provided by reacting compounds of **2** with **13** ($R'-O-C(O)-C(R^2R^3)-C(R^4R^5)-Halo$) instead of **3** under the same conditions as Scheme 1. R' of **13** is typically a C_1-C_6 alkyl (e.g., CH_3 , CH_2CH_3 , t-butyl, etc.). Also, **6** (e.g., 5-bromo-2-chloro-3-nitropyridine) can be reacted with a compound **15** ($R'-O-C(O)-C(R^2R^3)-C(R^4R^5)-R''$) (e.g., 3-hydroxy-propionic acid methyl ester), as in Scheme 2 to provide **12**. **12** can then be reduced as in Scheme 1 to provide **14**. **14** can also be provided by carrying out Scheme 2 using **2** and **15** as starting materials.

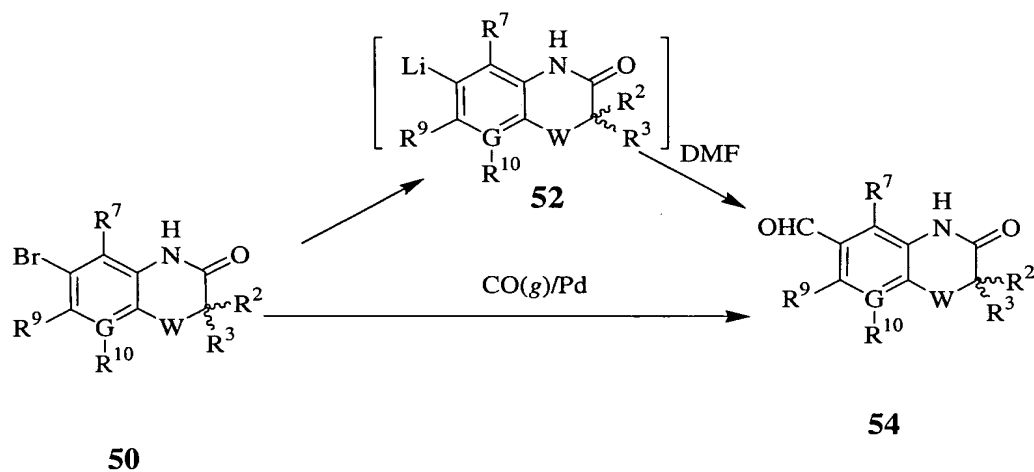
Scheme 4



The dihydro-quinoxalin-2-ones or pyrido[2,3-b]pyrazine-2-ones of formula **48** can be synthesized according to Scheme 4. **41** ($R^{21}HN-C(R^2R^3)-C(O)-O-R^{50}$ (e.g., sarcosine t-butyl ester) in acetonitrile with triethylamine is reacted with a 2-halonitrobenzene **40** (e.g., 2-fluoronitrobenzene) to yield **42** (e.g., methyl-(2-nitrophenyl)-amino]acetic acid tert-butylester). R^{50} typically is a C_1-C_6 alkyl (e.g., t-butyl). **42** in methanol is then treated with 20% Pd/C and subjected to a hydrogen atmosphere at a suitable pressure (e.g., 45 psi) to give **44** (e.g., 4-methyl-3,4-dihydro-1H-quinoxalin-2-one). **44** in acetic acid is then contacted with bromine in acetic acid to yield **46** (e.g., 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one). **46** is then reacted in DMF with sodium formate and bis(triphenylphosphine)palladium (II) dichloride in the presence of carbon monoxide to give **48** (e.g., 1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-

carbaldehyde). Alternatively, a compound of formula **43** ($R^{21}HN-C(R^2R^3)-C(R^4R^5)-C(O)-O-R^{50}$) can be reacted in a similar fashion with **40** to arrive at the corresponding benzo[b][1,4]diazepin-2-one or pyrido[3,4-b][1,4]diazepin-2-one.

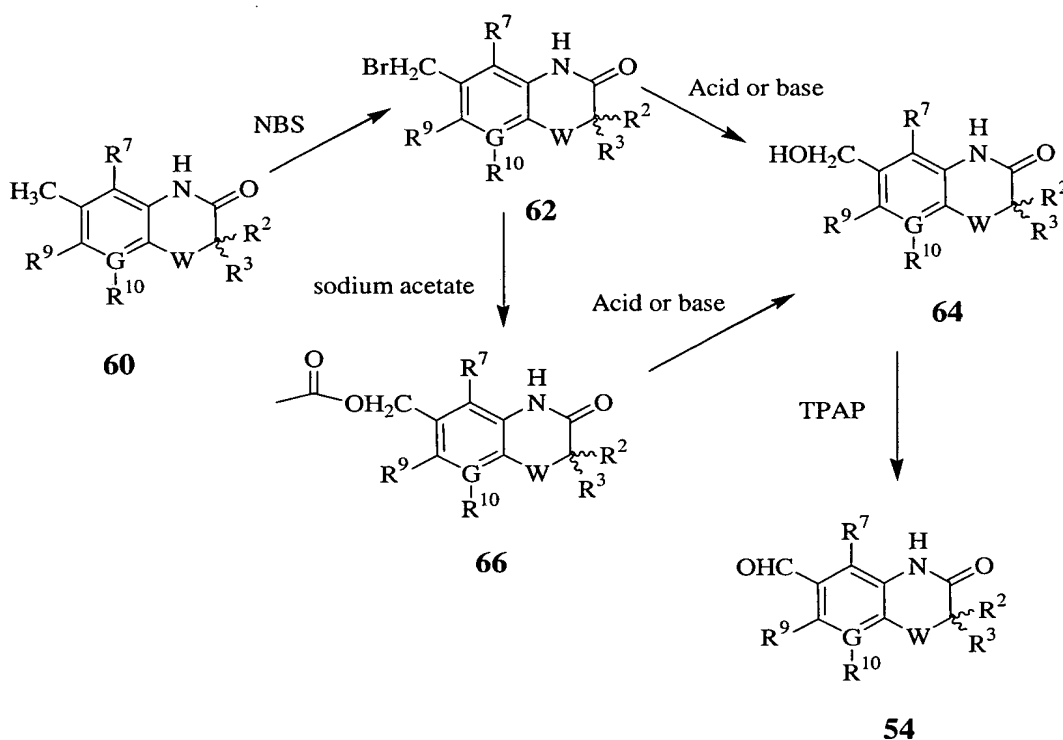
Scheme 5



When the J group is Br (e.g., **46** or **50**), the bromo group can be further reacted as in Scheme 5 with either an alkyl lithium reagent (e.g., t-butyl-Li) at a very low temperature (e.g., -70°C) in a nonprotic solvent (e.g., THF, ether, etc.) to elicit a bromine-lithium exchange to yield **52** in situ. **52** is then reacted with a dialkylformamide such as DMF (dimethylformamide) to give **54**. Alternatively, **50** can be reacted with CO(g) and a palladium catalyst to give **54** directly. The conversion of **50** to **54** can also be carried out using sodium formate and bis(triphenylphosphine)palladium (II) dichloride in the presence of carbon monoxide gas.

10

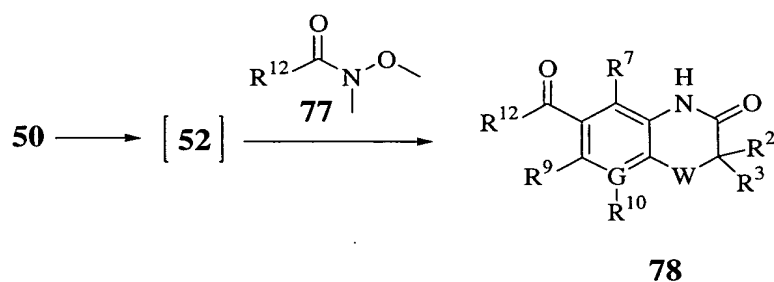
Scheme 6



When the J group is methyl (e.g., **60**), the methyl group can be halogenated as in Scheme 6 using a reagent such as NBS (*N*-Bromosuccinimide), NCS (*N*-chlorosuccinimide), or pyridinium bromide perbromide to yield the bromomethyl intermediate **62**. **62** can then be converted to the hydroxymethyl intermediate **64** by treatment with either aqueous acid or aqueous base.

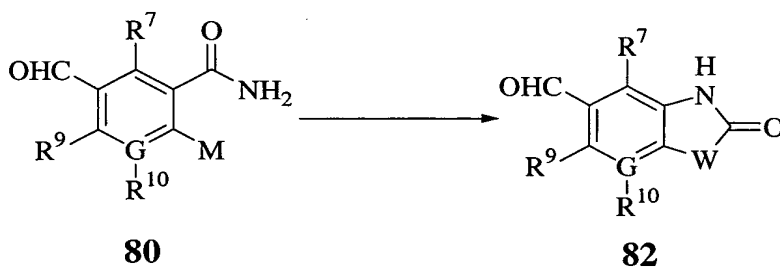
Alternatively, **62** can be reacted with sodium or potassium acetate to give the intermediate acetoxy derivative **66**, which can in turn be hydrolyzed with aqueous acid (e.g., acetic acid) or aqueous base to yield **64**. Compounds **64** can then be oxidized to the corresponding aldehydes, **54**, with an oxidizing reagent such as TPAP (tetrapropylammonium perruthenate), PCC (pyridinium chlorochromate), or PDC (pyridinium dichromate), or under conventional Moffatt oxidation conditions (e.g., DCC (*N,N'*-Dicyclohexylcarbodiimide) and DMSO), or Swern oxidation conditions (e.g., oxalyl chloride and DMSO).

Scheme 7



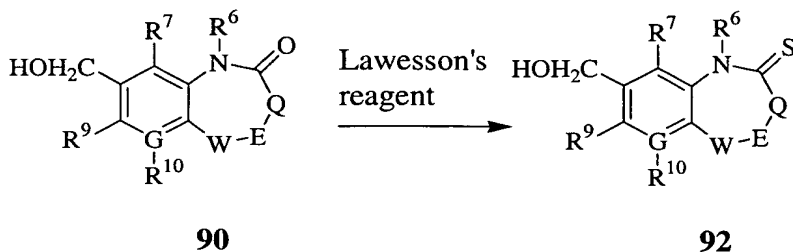
In Scheme 7, the compound **52** is reacted with **77** (R¹²-C(O)-N(OMe)(Me)) and then worked up with acid (e.g., HCl or citric acid, etc.) to arrive at **78**. An example of **77** is N-methoxy-N-methyl-acetamide. For the purposes of Scheme 7, R¹² is a C₁-C₆alkyl.

Scheme 8



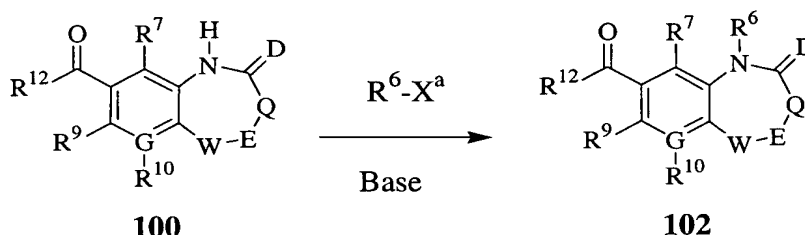
In Scheme 8, an appropriately substituted **80** (e.g., 5-formyl-2-hydroxybenzamide (Reich *et al.* *J. Med. Chem.*, 2000;43(9):1670-1683)) can be cyclized in a Hofmann reaction using a base (e.g., potassium hydroxide) and iodobenzene diacetate according to procedures such as those described in Prakash *et al.* *Synthesis*, 2000;4:541-543 to yield **82**. The M group of **80** can be OH, SH, or NR²¹.

Scheme 9



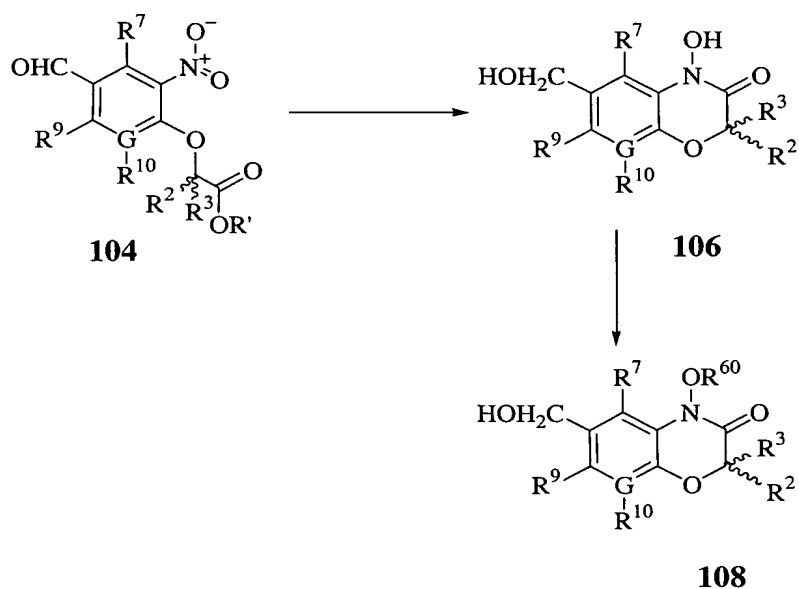
Compounds of formula **90** can then be transformed into the corresponding thione **92** as in Scheme 9 with Lawesson's reagent using procedures such as those described in Zhang et al. *Bioorg. & Med. Chem. Lett.*, 2001;11:2747-2750 or with P₄S₁₀ using methods that are known in the art. The hydroxymethyl group of **92** can be transformed into the corresponding aldehyde using the methods set out in Scheme 6.

Scheme 10



In Scheme 10, compounds such as **48**, **54**, or **100** can then be substituted with a compound of R⁶-X^a, where X^a is Halo, Cl, F, Br, or I, in the presence of a base such as potassium carbonate, cesium carbonate or 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazo-phosphorine on polystyrene in an organic solvent such as THF, DMF, or acetonitrile to yield intermediate **102**. Examples of compounds of R⁶-X^a include, but are not limited to, iodomethane, phenylethylbromide, methyl 3-(bromomethyl)benzoate, 2-(3,4-dichlorophenyl)ethyl bromide, cyclohexylmethyl bromide, 1-iodo-3-methylbutane, and 3-bromomethyl thiophene.

Scheme 11



Compounds of formula **108** can be synthesized using Scheme 11. A compound of **104** is reacted with NaBH_4 in a suspension of Pd/C to provide **106**.

106 is then reacted with $\text{R}^{60}\text{-X}^a$ (where X^a is a halogen) in the presence of K_2CO_3 in acetone to yield **108**. The hydroxymethyl group of **108** can be oxidized to the corresponding aldehyde using a reagent such as TPAP as in Scheme 6.

Examples of R^{60} include, but are not limited to a $\text{C}_1\text{-C}_6$ alkyl, an aryl, a

heteroaryl, a cycloalkyl, heterocycloalkyl, etc. Thus, examples of $\text{R}^{60}\text{-X}^a$

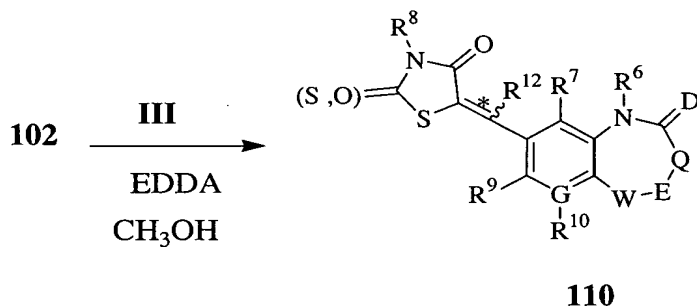
include, but are not limited to, iodomethane, phenylethylbromide, methyl

3-(bromomethyl)benzoate, 2-(3,4-dichlorophenyl)ethyl bromide,

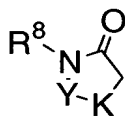
cyclohexylmethyl bromide, 1-iodo-3-methyl butane, and 3-bromomethyl

thiophene. A fluoro group as X^a is preferred in $\text{R}^{60}\text{-X}^a$, if R^{60} is a heteroaryl or aryl that is directly attached to X^a .

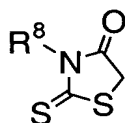
Scheme 12



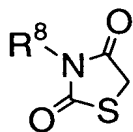
In Scheme 12, **102**, is reacted with a compound of Formula III containing an activated methylene group, for example: a rhodanine (e.g., rhodanine, rhodanine-3-acetic acid, 3-phenyl rhodanine, etc.) or a thiazolidinedione (e.g., thiazolidinedione, etc.), in the presence of an organic base, such as ethylenediamine diacetate (EDDA), diisopropylethylamine, sodium acetate or pyridine, in the presence of acetic acid and methanol to form a compound **110**. Compounds of Formula III are defined herein as a compound having the following structure:



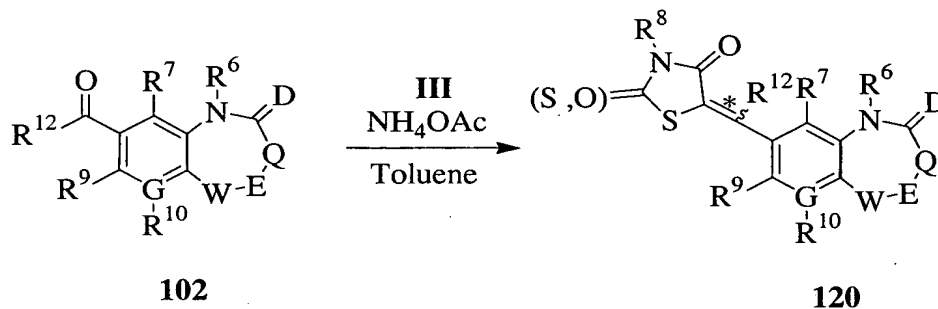
where Y is C(O) or C(S), and K is S. Examples of compounds of Formula III include rhodanine and rhodanine derivatives:



and thiazolidine dione and thiazolidine dione derivatives:

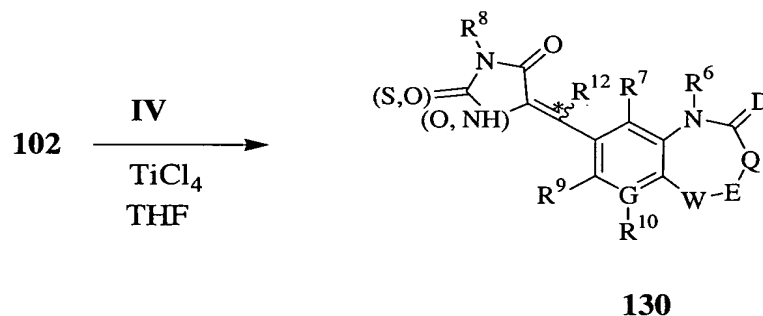


Scheme 13

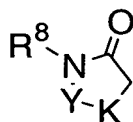


Alternatively, in Scheme 13 a Knoevenagel condensation of the active methylene of Formula III with **102** can be carried out to yield **110**, using ammonium acetate in toluene and heating to a high temperature (e.g., 110°C), according to procedures such as those described in Lee and Sun, *Tetrahedron Lett.*, 2000;41:5729-5732. When R^{12} of **102** is H, then the reaction generally can proceed without ammonium acetate (see Zhang and Sun, *supra*, 2000).

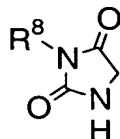
Scheme 14



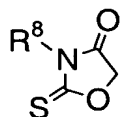
In Scheme 14, **102** is reacted with a compound of Formula IV, such as a imidazolidine-2,4-dione or a 2-thioxo-oxazolidin-4-one, or a 2-thioxo-imidazolidin-4-one in the presence of titanium tetrachloride ($TiCl_4$) and pyridine in THF to form a compound of formula **130**. Compounds of Formula IV are defined herein in a compound having the following structure:



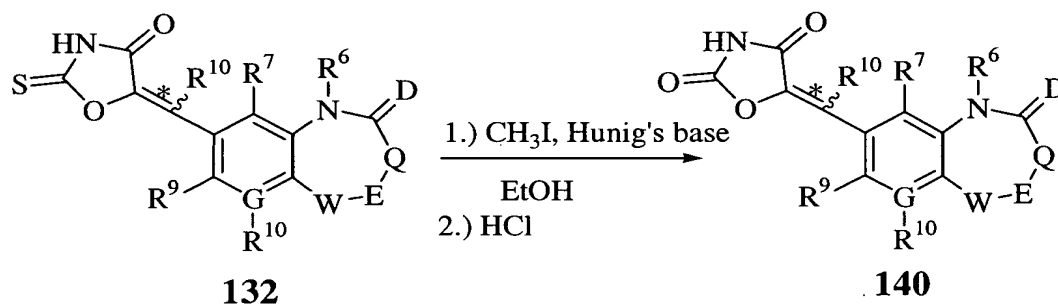
where Y is C(O) or C(S), and K is O or NH. Examples of compounds of Formula IV include imidazolidine-2,4-dione and imidazolidine-2,4-dione derivatives:



5 and 2-thioxo-oxazolidin-4-one and 2-thioxo-oxazolidin-4-one derivatives:

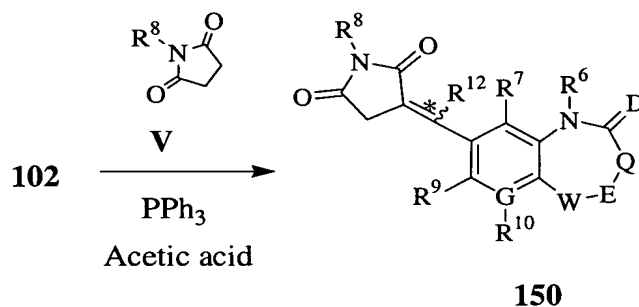


Scheme 15

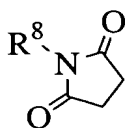


10 A 2-thioxo-oxazolidin-4-one derivative **132** obtained using Scheme 14 can be converted to an oxazolidine-2,4-dione **140** with iodomethane and Hunig's base in ethanol, followed by concentrated HCl as depicted in Scheme 15.

Scheme 16



15 In Scheme 16, **102** is reacted with a compound of Formula V, such as a pyrrolidine-2,5-dione in the presence of triphenylphosphine (PPh₃) and acetic acid (AcOH) to form a compound of the formula **150**. Compounds of Formula V are defined herein in a compound having the following structure:



III. EVALUATION OF COMPOUNDS

Compounds of the present invention (e.g., compounds of Formula I and pharmaceutically acceptable salts thereof) can be assayed for their ability to inhibit a PI3K. Examples of these assays are set out below and include in vitro and in vivo assays of PI3K activity.

In certain embodiments of the present invention are compounds that selectively inhibit one or more PI3Ks as compared to one or more enzymes including, but not limited to, a cyclic nucleotide dependent protein kinase, PDGF, a tyrosine kinase, a MAP kinase, a MAP kinase kinase, a MEKK, a cyclin-dependent protein kinase. In other embodiments of the invention are compounds that selectively inhibit one PI3K as compared to another PI3K. For example, in certain embodiments, compounds of the present invention display the ability to selectively inhibit PI3K γ as compared to PI3K α or PI3K β . A compound selectively inhibits a first enzyme as compared to a second enzyme, when the IC₅₀ of the compound towards the first enzyme is less than the IC₅₀ of the compound towards the second compound. The IC₅₀ can be measured, for example, in an in vitro PI3K assay.

In presently preferred embodiments, compounds of the present invention can be assessed for their ability to inhibit PI3K activity in an in vitro or an in vivo assay (see below).

PI3K assays are carried out in the presence or absence of a PI3K inhibitory compound, and the amount of enzyme activity is compared for a determination of inhibitory activity of the PI3K inhibitory compound.

Samples that do not contain a PI3K inhibitory compound are assigned a relative PI3K activity value of 100. Inhibition of PI3K activity is achieved when the PI3K activity in the presence of a PI3K inhibitory compound is less than the control sample (i.e., no inhibitory compound). The IC₅₀ of a compound is the concentration of compound that exhibits 50% of the control sample activity. In

certain embodiments, compounds of the present invention have an IC₅₀ of less than about 100 μM. In other embodiments, compounds of the present invention have an IC₅₀ of about 1 μM or less. In still other embodiments, compounds of the present invention have an IC₅₀ of about 200 nM or less.

5 PI3Kγ assays have been described in the art (see e.g., Leopoldt et al. *J. Biol. Chem.*, 1998;273:7024-7029). Typically, a sample containing a complex of p101 and p110γ protein are combined with Gβ and Gγ proteins (e.g., G protein β₁/γ₂ subunits). Radiolabeled ATP (e.g., γ-³²P-ATP) is then added to this mixture. The lipid substrates are formed by creating PIP₂ containing lipid
10 micelles. The reactions are then started by adding the lipid and enzyme mixtures and are stopped with the addition of H₃PO₄. The lipid products are then transferred to a glass fiber filter plate, and washed with H₃PO₄ several times. The presence of radioactive lipid product (PIP₃) can be measured using radiometric methods that are well-known in the art.

15 The activity of growth factor regulated PI3Ks can also be measured using a lipid kinase assay. For example, PI3Kα can be assayed using samples that contain a regulatory and a catalytic subunit. An activating peptide (e.g., pY peptide, SynPep Corp.) is added to the sample with radiolabeled ATP. PIP₂ containing lipid micelles are then added to the sample to start the reaction. The reactions are
20 worked up and analyzed as described for the PI3Kγ assay just described. Assays can also be carried out using cellular extracts (Susa et al. *J. Biol. Chem.*, 1992;267:22951-22956).

IV. PHARMACEUTICAL COMPOSITIONS

25 The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and a compound of the present invention (e.g., a compound of Formula I, or a pharmaceutically acceptable salt thereof). A compound of the present invention can be formulated as a pharmaceutical composition in the form of a syrup, an elixir, a suspension, a powder, a granule, a tablet, a capsule, a lozenge, a troche, an aqueous solution, a
30 cream, an ointment, a lotion, a gel, an emulsion, etc. Preferably, a compound of

the present invention will cause a decrease in symptoms or a disease indicia associated with a PI3K-mediated disorder as measured quantitatively or qualitatively.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets contain from 1% to 95% (w/w) of the active compound. In certain embodiments, the active compound ranges from 5% to 70% (w/w). Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, preferably 1.0 mg to 100 mg, or from 1% to 95% (w/w) of a unit dose, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention (see, e.g., *Remington: The Science and Practice of Pharmacy*, 20th ed., Gennaro et al. Eds., Lippincott Williams and Wilkins, 2000).

A compound of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations (i.e., they can be “nebulized”) to be administered via inhalation. Aerosol formulations can be

placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane nitrogen, and the like.

Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include
5 aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can
10 be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

15 The dose administered to a subject, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the subject over time. The dose will be determined by the efficacy of the particular compound employed and the condition of the subject, as well as the body weight or surface area of the subject to be treated. The size of the dose also will be determined by
20 the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular subject. In determining the effective amount of the compound to be administered in the treatment or prophylaxis of the disorder being treated, the physician can evaluate factors such as the circulating plasma levels of the compound, compound toxicities, and/or the
25 progression of the disease, etc. In general, the dose equivalent of a compound is from about 1 $\mu\text{g/kg}$ to 10 mg/kg for a typical subject. Many different administration methods are known to those of skill in the art.

For administration, compounds of the present invention can be administered at a rate determined by factors that can include, but are not limited to, the LD_{50} of the compound, the pharmacokinetic profile of the compound,
30 contraindicated drugs, and the side-effects of the compound at various

concentrations, as applied to the mass and overall health of the subject.

Administration can be accomplished via single or divided doses.

V. METHODS FOR TREATING OR PREVENTING PI3K-MEDIATED DISORDERS AND CONDITIONS

5 The compounds of the present invention and pharmaceutical compositions comprising a compound of the present invention can be administered to a subject suffering from a PI3K-mediated disorder or condition. PI3K-mediated disorders and conditions can be treated prophylactically, acutely, and chronically using compounds of the present invention, depending on the nature of the disorder or
10 condition. Typically, the host or subject in each of these methods is human, although other mammals can also benefit from the administration of a compound of the present invention.

 In therapeutic applications, the compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms.
15 Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. In certain
20 embodiments, the compounds of the present invention are delivered orally. The compounds can also be delivered rectally, buccally or by insufflation.

 The compounds utilized in the pharmaceutical method of the invention can be administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. In certain embodiments, the daily dose range is from about 0.1 mg/kg to
25 about 10 mg/kg. The dosages, however, may be varied depending upon the requirements of the subject, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound.
30 Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The compounds of the invention can also be combined in a pharmaceutical composition with compounds that are useful for the treatment of cancer (e.g., cytotoxic drugs such as TAXOL®, taxotere, GLEEVEC® (Imatinib Mesylate), adriamycin, daunomycin, cisplatin, etoposide, a vinca alkaloid, vinblastine, vincristine, methotrexate, or adriamycin, daunomycin, cis-platinum, etoposide, and alkaloids, such as vincristine, farnesyl transferase inhibitors, endostatin and angiostatin, VEGF inhibitors, and antimetabolites such as methotrexate. The compounds of the present invention may also be used in combination with a taxane derivative, a platinum coordination complex, a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or an aromatase inhibitor).

The compounds of the invention can also be combined in a pharmaceutical composition with compounds that are useful for the treatment of a thrombolytic disease, heart disease, stroke, etc., (e.g., aspirin, streptokinase, tissue plasminogen activator, urokinase, anticoagulants, antiplatelet drugs (e.g., PLAVIX®; clopidogrel bisulfate), a statin (e.g., LIPITOR® (Atorvastatin calcium), ZOCOR® (Simvastatin), CRESTOR® (Rosuvastatin), etc.), a Beta blocker (e.g. Atenolol), NORVASC® (amlodipine besylate), and an ACE inhibitor (e.g., lisinopril)).

The compounds of the invention can also be combined in a pharmaceutical composition with compounds that are useful for the treatment of antihypertension agents such as, ACE inhibitors, lipid lowering agents such as statins, LIPITOR® (Atorvastatin calcium), calcium channel blockers such as NORVASC® (amlodipine besylate). The compounds of the present invention may also be used in combination with fibrates, beta-blockers, NEPI inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

For the treatment of inflammatory diseases, including rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF α monoclonal antibodies (such as REMICADE®, CDP-870 and D2E7 (HUMIRA®) and TNF receptor immunoglobulin fusion molecules (such as ENBREL®), IL-1 inhibitors, receptor antagonists or soluble IL-1R α (e.g. KINERET™ or ICE inhibitors), nonsteroidal anti-inflammatory agents (NSAIDS), piroxicam, diclofenac, naproxen, flurbiprofen, fenoprofen, ketoprofen ibuprofen, fenamates, mefenamic acid, indomethacin, sulindac,

apazone, pyrazolones, phenylbutazone, aspirin, COX-2 inhibitors (such as CELEBREX® (celecoxib), VIOXX® (rofecoxib), BEXTRA® (valdecoxib and etoricoxib), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2X7 inhibitors, $\alpha 2\delta$ inhibitors, NEUROTIN®, pregabalin, low dose
5 methotrexate, leflunomide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents
10 (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such
15 as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptics compounds such as Valant.

The compounds of the present invention may also be used in combination
20 with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such
25 as donepezil, tacrine, $\alpha 2\delta$ inhibitors, NEUROTIN®, pregabalin, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as EVISTA® (raloxifene hydrochloride) droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-
30 506 and rapamycin.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light

thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

EXAMPLES

5 Intermediate 1: **(4-Formyl-2-nitro-phenoxy)-acetic acid ethyl ester**. To a solution of 4-hydroxy-3-nitrobenzaldehyde (10.0 g, 59.8 mmol) in tetrahydrofuran (600 mL) and DMF (240 mL) was added dry sodium hydride (1.58 g, 65.82 mmol) and ethyl bromoacetate (7.30 mL, 65.82 mmol). The reaction was refluxed for 24 hours. The reaction was then concentrated and diluted with ethyl acetate (500 mL) and acidified to pH 2 with 1N HCl. The organic layer was then washed
10 with saturated sodium bicarbonate (2 × 200 mL), sodium chloride (2 × 200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a dark red oil. The oil was used in the next step without purification. ¹H NMR (d₆-DMSO) δ 1.18 (t, 3H), 4.15 (q, 2H), 5.14 (s, 2H), 7.49 (d, 1H), 8.11 (dd, 1H), 8.41 (s, 1H), 9.93 (s, 1H). MS: M⁺-1=252.1 Da.

15 Intermediate 2: **6-Hydroxymethyl-4H-1,4-benzoxazin-3-one**. To a solution of intermediate 1 (6.40 g, 1.67 mmol) in methanol (100 mL) was added Raney nickel (3.0 g). The reaction was then pressurized under an atmosphere of hydrogen to 48 psi for 23 hours. The solution was then filtered through a pad of celite. The celite cake was washed with methanol (200 mL) and concentrated under reduced
20 pressure to yield a brown solid. ¹H NMR (d₆-DMSO) δ 4.36 (s, 2H), 4.50 (s, 2H), 5.12 (s, 1H), 6.62-6.86 (m, 3H). MS: M⁺-1=178.1 Da.

Intermediate 3: **3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. To a solution of intermediate 2 (2.0 g, 11.2 mmol) in dichloromethane (80 mL) at room temperature was added pyridinium dichromate (6.31 g, 16.8 mmol). The
25 reaction was stirred for 24 hours. The reaction mixture was then filtered through a pad of celite. The celite cake was washed with ethyl ether (100 mL) and ethyl acetate (100 mL). The solution was then concentrated under reduced pressure to yield a dark red solid. ¹H NMR (d₆-DMSO) δ 4.67 (s, 2H), 7.09 (d, 1H), 7.33 (s, 1H), 7.49 (d, 1H), 9.79 (s, 1H). MS: M⁺-1=175.9 Da.

Example 1: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-**

benzoxazin-3-one. To a solution of intermediate 3 (0.100 g, 0.565 mmol) in 30 mL of methanol was added ethylenediamine diacetate (EDDA) (0.101 g, 0.565 mmol) followed by rhodanine (0.075 g, 0.565 mmol). The solution was stirred at room temperature for 14 hours, and the resulting yellow precipitate was isolated by filtration, washed with methanol (50 mL) and diethyl ether (50 mL). The solid was air dried to provide the title compound. Microanalysis ($C_{12}H_8N_2O_3S_2$): calculated: C=49.30, H=2.76, N=9.58; found: C=47.96, H=2.80, N=9.17. MS: $M^+-1=291.0$ Da.

Intermediate 4: **4-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-**

carbaldehyde. To an acetonitrile (20 mL) solution of intermediate 3 (0.202 g, 1.7 mmol) was added iodomethane (0.127 mL, 20.5 mmol), potassium carbonate (0.587 g, 4.25 mmol) followed by benzyltriethylammonium chloride (0.193 g, 0.847 mmol). The reaction was heated to reflux for 4 hours then cooled. The solvent was removed under reduced pressure, and the resulting residue was diluted with ethyl acetate (50 mL) and 1N hydrochloric acid (50 mL). The layers were separated and the organic layer was washed with 1N hydrochloric acid (25 mL), saturated $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a white solid. 1H NMR ($CDCl_3$) δ 3.42 (s, 3H), 4.72 (s, 2H), 7.11 (d, 1H), 7.52-7.55 (m, 2H), 9.91 (s, 1H) ppm. MS: $M^+-1=191.1$ Da.

Example 2: **4-Methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-**

benzoxazin-3-one. The title compound was synthesized in a manner analogous to Example 1, from intermediate 4. 1H NMR (d_6 -DMSO) δ 2.48 (s, 3H), 4.73 (s, 2H), 7.12 (d, 1H), 7.21 (d, 1H), 7.37 (s, 1H), 7.61 (s, 1H). MS: $M^+-1=305.0$ Da.

Unless otherwise noted, the following examples were synthesized in a manner analogous to Example 2.

Intermediate 5: **(6-Formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid tert-butyl ester.** The title compound was synthesized in a manner analogous to

intermediate 4 using intermediate 3 and *tert*-butyl bromoacetate. MS:

$M^+-1=291.2$ Da.

Intermediate 6: **[3-Oxo-6-(4-oxo-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydr-benzo[1,4]oxazin-4-yl]-acetic acid *tert*-butyl ester**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 5. MS:

$M^+-1=405.1$ Da.

Example 3: **[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-yl]-acetic acid**. To solution of intermediate 6 (0.150 g, 0.369 mmol) in dichloromethane (18 mL) at room temperature was added trifluoroacetic acid (6 mL). The solution was stirred for 4.5 hours. The yellow precipitate was isolated by filtration, washed with methanol (50 mL) and diethyl ether (50 mL). The solid was air dried to provide the title compound. ^1H NMR (d_6 -DMSO) δ 4.65 (s, 2H), 4.80 (s, 2H), 7.16 (d, 1H), 7.22 (d, 1H), 7.32 (dd, 1H), 7.58 (s, 1H). MS: $M^+-1=349.0$ Da.

Example 4: **4-Benzyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2$): calculated: C=59.67, H=3.69, N=7.32; found: C=59.07, H=3.92, N=7.25. MS: $M^+-1=381.1$ Da.

Example 5: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-phenethyl-4H-1,4-benzoxazin-3-one**. Microanalysis ($\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$): calculated: C=60.59, H=4.07, N=7.07; found: C=60.02, H=4.16, N=6.86. MS: $M^+-1=395.1$ Da.

Intermediate 7: **(4-Formyl-2-methoxy-6-nitro-phenoxy)-acetic acid ethyl ester**.

To a room temperature solution of 5-nitrovanillin (2.00 g, 10.11 mmol) in tetrahydrofuran (100 mL) was added ethyl glycolate (0.960 mL, 10.11 mmol), triphenylphosphine (3.84 g, 14.65 mmol), and dropwise addition of diethyl azodicarboxylate (2.70 mL, 17.10 mmol). The reaction was stirred overnight at room temperature. The solution was then concentrated in under reduced pressure to yield a crude oil. Purification of the residue by silica gel flash chromatography (20% ethyl acetate/hexane to 40% ethyl acetate/hexane) afforded the title

compound. ^1H NMR (d_6 -DMSO) δ 1.15 (t, 3H), 3.94 (s, 3H), 4.10 (q, 2H), 4.93 (s, 2H), 7.79 (d, 1H), 8.02 (d, 1H), 9.94 (s, 1H). MS: $\text{M}^+ + 1 = 284.2$ Da.

Intermediate 8: **8-methoxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 2 and intermediate 3 using intermediate 7. MS: $\text{M}^+ - 1 = 206.1$ Da.

Example 6: **8-Methoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 8. ^1H NMR (d_6 -DMSO) δ 3.80 (s, 3H), 4.62 (s, 2H), 6.74 (d, 1H), 7.01 (s, 1H), 7.49 (s, 1H), 10.82 (s, 1H). MS: $\text{M}^+ - 1 = 321.1$ Da.

Example 7: **[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-yl]-acetic acid methyl ester**. ^1H NMR (d_6 -DMSO) δ 3.71 (s, 3H), 4.78 (s, 2H), 4.82 (s, 2H), 7.17-7.23 (m, 2H), 7.34 (d, 1H), 7.60 (s, 1H). MS: $\text{M}^+ - 1 = 362.9$ Da.

Example 8: **3-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoic acid methyl ester**. ^1H NMR (d_6 -DMSO) δ 3.82 (s, 3H), 4.94 (s, 2H), 5.27 (s, 2H), 7.10 (s, 1H), 7.15-7.26 (m, 2H), 7.46-7.55 (m, 3H), 7.86 (d, 1H), 7.98 (s, 1H). MS: $\text{M}^+ - 1 = 440.0$ Da.

Example 9: **4-Biphenyl-4-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($\text{C}_{25}\text{H}_{18}\text{N}_2\text{O}_3\text{S}_2$): calculated: C=65.48, H=3.96, N=6.11; found: C=66.04, H=4.36, N=5.98. MS: $\text{M}^+ - 1 = 457.1$ Da.

Example 10: **[4-Oxo-5-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-2-thioxo-thiazolidin-3-yl]-acetic acid; compound with trifluoroacetic acid**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 3 and substituting rhodanine-3-acetic acid for

rhodanine. ^1H NMR (d_6 -DMSO) δ 4.69 (s, 2H), 4.72 (s, 2H), 7.10 (d, 1H), 7.16 (s, 1H), 7.31-7.34 (m, 1H), 7.79 (s, 1H), 10.90 (s, 1H), 13.45 (bs, 1H). MS: $M^+-1=457.1$ Da.

Example 11: **4-Naphthalen-2-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. ^1H NMR (d_6 -DMSO) δ 4.97 (s, 2H), 5.35 (s, 2H), 7.105-7.23 (m, 3H), 7.43-7.47 (m, 4H), 7.84-7.91 (m, 4H), 13.68 (bs, 1H). MS: $M^+-1=431.1$ Da.

Example 12: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-pyridin-3-ylmethyl-4H-1,4-benzoxazin-3-one**. ^1H NMR (d_6 -DMSO) δ 4.92 (s, 2H), 5.21 (s, 2H), 7.08-7.22 (m, 3H), 7.34-7.37 (m, 1H), 7.52 (s, 1H), 7.71 (d, 1H), 8.47 (d, 1H), 8.59 (s, 1H). MS: $M^+-1=383.2$ Da.

Intermediate 9: **(S)-2-(4-Formyl-2-nitro-phenoxy)-propionic acid methyl ester**. The title compound was synthesized in a manner analogous to intermediate 7 using 4-hydroxy-3-nitrobenzaldehyde and methyl (*R*)-(+)-lactate instead of 5-nitrovanillin and ethyl glycolate. MS: $M^+-87=166.1$ Da.

Intermediate 10: **(S) 2-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 2 and intermediate 3 using intermediate 9 as starting material.

Example 13: **(S)-2-Methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 10. ^1H NMR (d_6 -DMSO) δ 1.42 (d, 3H), 4.76-4.81 (q, 1H), 7.08 (m, 2H), 7.23-7.26 (m, 1H), 7.53 (s, 1H). MS: $M^+-1=305.1$ Da.

Example 14: **4-(3,5-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. ^1H NMR (d_6 -DMSO) δ 2.20 (s, 6H), 4.89 (s, 2H), 5.06 (s, 2H), 6.86 (d, 3H), 6.96 (s, 1H), 7.10 (d, 1H), 7.23 (d, 1H), 7.43 (s, 1H). MS: $M^+-1=409.0$ Da.

Example 15: **4-(3-Benzoyloxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{26}H_{20}N_2O_4S_2$): calculated: C=63.92, H=4.13, N=5.73; found: C=63.88, H=4.14, N=5.74. MS: $M^+-1=487.2$ Da.

5 Intermediate 11: **4-Hydroxy-2,5-dimethyl-3-nitro-benzaldehyde**. To a -10°C (ice and sodium chloride) solution of 4-hydroxy-2,5-dimethylbenzaldehyde (1.0 g, 6.65 mmol) in concentrated sulfuric acid (10 mL) was added dropwise 70% (concentrated) nitric acid (0.598 g, 6.65 mmol) in 2 mL concentrated sulfuric acid. The reaction stirred for approximately 30 minutes. The reaction was then poured
10 onto crushed ice. The precipitate was collected and washed with water. The solid was then dried on a high vacuum pump to yield a white solid. Microanalysis ($C_9H_9N_1O_4$): calculated: C=55.39, H=4.65, N=7.18; found: C=55.60, H=4.65, N=7.02. MS: $M^+-1=194.1$ Da.

Intermediate 12: **(4-Formyl-3,6-dimethyl-2-nitro-phenoxy)-acetic acid ethyl ester**. The title compound was synthesized in a manner analogous to
15 intermediate 7 using intermediate 11. Microanalysis ($C_{13}H_{15}N_1O_6$): calculated: C=55.51, H=5.38, N=4.98; found: C=55.60, H=5.30, N=4.94. MS: $M^++1=282.2$ Da.

Intermediate 13: **5,8-Dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to
20 intermediate 10 using intermediate 12. MS: $M^++1=204.1$ Da.

Example 16: **5,8-Dimethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 starting from intermediate 13. ^1H NMR (d_6 -DMSO)
25 δ 2.17 (s, 3H), 2.23 (s, 3H), 4.59 (s, 2H), 6.87 (s, 1H), 7.65 (s, 1H), 10.33 (s, 1H). MS: $M^+-1=319.1$ Da.

Intermediate 14: **3-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazine-4-ylmethyl)-benzoic acid methyl ester**. The title compound was synthesized in a

manner analogous to intermediate 4 using intermediate 3 and methyl 3-(bromomethyl)benzoate. MS: $M^+-1=325.1$ Da.

Intermediate 15: **3-(6-Formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-benzoic acid**. To a tetrahydrofuran solution (25 mL) of intermediate 14 was added 1N lithium hydroxide (2.67 mL, 2.67 mmol). The solution was stirred at room temperature for 7 hours. The reaction was concentrated under reduced pressure and then diluted with ethyl acetate (200 mL) and 1 M hydrochloric acid (25 mL). The layers were separated and the organic layer was washed with saturated sodium chloride (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product. Purification of the residue by silica gel flash chromatography (50% ethyl acetate/hexane 1% acetic acid) afforded the title compound as a solid. Microanalysis ($C_{17}H_{13}N_1O_5$): calculated: C=65.59, H=4.21, N=4.50; found: C=65.14, H=4.36, N=4.13. MS: $M^+-1=310.2$ Da.

Example 17: **3-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoic acid**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 15. Microanalysis ($C_{20}H_{14}N_2O_5S_2$): calculated: C=56.33, H=3.31, N=6.57; found: C=55.33, H=3.22, N=6.54. 1H NMR (d_6 -DMSO) δ 4.94 (s, 1H), 5.25 (s, 1H), 7.14-7.22 (m, 3H), 7.43-7.56 (m, 3H), 7.82 (d, 2H), 7.88 (s, 1H), 12.96 (bs, 1H).

Example 18: **(S)-4-Benzyl-2-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 2 using intermediate 10. Microanalysis ($C_{20}H_{16}N_2O_3S_2$): calculated: C=60.59, H=4.07, N=7.07; found: C=60.61, H=4.29, N=6.72. MS: $M^+-1=396.2$ Da.

Intermediate 16: **3-Oxo-4-(bromomethyl-benzyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. Cesium carbonate (3.66 g, 11.23 mmol, 2 equiv) was added to a solution of intermediate 3 (0.984 g, 5.56 mmol) and α,α' -dibromo-*p*-xylene (11.89 g, 45.03 mmol, 8.1 equiv) in dimethylformamide (135 mL). The resulting suspension was stirred at room temperature for 15 hours.

The reaction was filtered, the solids were rinsed with DMF, and the resulting filtrate was concentrated to a yellow solid. The residue was dissolved in ethyl acetate and 1 M HCl. The organic layer was separated, washed with H₂O and brine, dried over MgSO₄, and concentrated to a pale yellow solid. Flash chromatography of the crude product (SiO₂, dichloromethane then 5% diethyl ether in dichloromethane) provided the title compound. ¹H NMR (DMSO-d₆) δ 4.66 (s, 2H), 4.93 (s, 2H), 5.20 (s, 2H) 7.21 (d, 1H), 7.29 (d, 2H), 7.40 (d, 2H) 7.46 (d, 1H), 7.58 (dd, 1H), 9.78 (s, 1H).

Intermediate 17: **3-Oxo-4-(4-piperidin-1-ylmethyl-benzyl)-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. Piperidine (0.200 mL, 2.02 mmol, 2 equiv) was added to a solution intermediate 16 (0.396 g, 1.00 mmol) in CH₂Cl₂ (50 mL). The reaction was stirred 18 hours then concentrated to a yellow residue that was partitioned between Et₂O and H₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated to a clear, colorless oil which was used without further purification.

Example 19: **4-(4-Piperidin-1-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 starting from intermediate 17. ¹H NMR (DMF-d₇) δ 1.05-1.15 (m, 2H), 1.25-1.32 (m, 4H), 2.40-2.60 (m, 4H), 3.69 (bs, 2H), 4.54 (s, 2H), 4.92 (s, 2H), 6.71-6.74 (m, 2H), 6.81-6.82 (m, 2H), 7.06 (s, 4H). MS: M⁺ + 1 = 480.3 Da.

Example 20: **4-(4-Morpholin-4-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMF-d₇) δ 2.42 (s, 4H), 3.55 (s, 2H), 3.58 (s, 4H), 4.98 (s, 2H), 5.30 (s, 2H), 7.17-7.19 (m, 2H), 7.28-7.40 (m, 5H), 7.47 (s, 1H). MS: M⁺-1 = 480.1 Da.

Example 21: **4-(4-Diethylaminomethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was

synthesized in a manner analogous to Example 19. ¹H NMR (DMF-d₇) δ 1.12 (t, 6H), 3.02-3.03 (m, 4H), 4.20 (s, 2H), 4.94 (s, 2H), 5.31 (s, 2H), 7.11-7.14 (m, 2H), 7.20-7.22 (m, 2H), 7.47 (d, 2H), 7.52 (d, 2H). MS: M⁺-1=466.1 Da.

Example 22: **Acetic acid 2-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzyl ester.**

¹H NMR (DMSO-d₆) δ 2.06 (s, 3H), 4.95 (s, 2H), 5.22 (s, 2H), 5.27 (s, 2H), 6.94-7.27 (m, 6H), 7.45 (s, 2H). MS: M⁺-1=453.0 Da.

Example 23: **4-(4-Benzyloxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** ¹H NMR (DMSO-d₆) δ 4.89 (s, 2H), 5.05 (s, 2H), 5.10 (s, 2H), 6.96 (d, 2H), 7.12-7.40 (m, 10H), 7.51 (s, 1H). MS: M⁺-1=487.1 Da.

Intermediate 18: **Acetic acid 2-(6-formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzyl ester.** The title compound was synthesized in a manner analogous to intermediate 4 using intermediate 3 and acetic acid 2-bromomethyl-benzyl bromide. MS: M⁺-1=339.1 Da.

Example 24: **4-(2-Hydroxymethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** To a room temperature tetrahydrofuran solution (50 mL) of intermediate 18 was added 1N lithium hydroxide (0.58 mL, 0.58 mmol). The reaction was stirred overnight at room temperature. The solution was then diluted with ethyl acetate (200 mL) and acidified to pH 2 with 1N hydrochloric acid. The organic layer was separated and washed with H₂O (50 mL) and saturated sodium chloride (50 mL). The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure to the crude product. Purification of the residue by silica gel flash chromatography (45% ethyl acetate/hexane) afforded 4-(2-hydroxymethyl-benzyl)-4H-benzo[1,4]oxazine-3-one. MS: M⁺-1=297.1 Da. The title compound was synthesized in a manner analogous to Example 1 using the above

intermediate. Microanalysis (C₂₀H₁₆N₂O₄S₂): calculated: C=58.24, H=3.91, N=6.79; found: C=57.89, H=4.10, N=6.70. MS: M⁺-1=412.0 Da.

Example 25: **4-[4-(Naphthalen-1-yloxy)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis (C₂₉H₂₀N₂O₄S₂):
5 calculated: C=66.40, H=3.84, N=5.34; found: C=66.24, H=3.74, N=5.15. MS:
M⁺-1=523.1 Da.

Example 26: **4-(3,5-Dimethoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis (C₂₁H₁₈N₂O₅S₂):
10 calculated: C=57.00, H=4.10, N=6.33; found: C=57.08, H=4.00, N=6.09. MS:
M⁺-1=441.0 Da.

Example 27: **4-[4-((2S,6R)-2,6-Dimethyl-piperidin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title
compound was synthesized in a manner analogous to Example 19. ¹H NMR
(DMSO-d₆) δ 1.29-2.94 (m, 12H), 4.29 (bs, 2H), 4.87 (bs, 2H), 5.19 (bs, 2H),
15 6.97-7.14 (m, 4H), 7.36-7.48 (m, 4H). MS: M⁺-1=506.1 Da.

Intermediate 19: **(4-Formyl-2-methyl-6-nitro-phenoxy)-acetic acid ethyl ester**.
4-Hydroxy-3-methyl-5-nitro-benzaldehyde was synthesized in a manner
analogous to intermediate 11 by using 4-hydroxy-3-methylbenzaldehyde instead
of 4-hydroxy-2,5-dimethylbenzaldehyde. The title compound was synthesized in
20 a manner analogous to intermediate 9 using 4-hydroxy-3-methyl-5-nitro-
benzaldehyde instead of 5-nitrovanillin. MS: M⁺+1=268.2 Da.

Intermediate 20: **8-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to
intermediate 2 and intermediate 3 using intermediate 19 as starting material. MS:
25 M⁺-1=190.1 Da.

Intermediate 21: **4-(3,5-Dimethyl-benzyl)-8-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner

analogous to intermediate 4 using intermediate 20 and 3,5-dimethylbenzyl bromide. MS: $M^+-1=308.1$ Da.

5 Example 28: **4-(3,5-Dimethyl-benzyl)-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 21. Microanalysis ($C_{22}H_{20}N_2O_3S_2$): calculated: C=62.24, H=4.75, N=6.60; found: C=62.22, H=4.83, N=6.48. MS: $M^+-1=423.1$ Da.

10 Example 29: **4-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{21}H_{12}N_2F_6O_3S_2$): calculated: C=48.65, H=2.33, N=5.40; found: C=48.52, H=2.43, N=5.21. MS: $M^+-1=517.0$ Da.

15 Example 30: **4-[2-(3,5-Dimethylphenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{22}H_{20}N_2O_3S_2$): calculated: C=62.24, H=4.75, N=6.60; found: C=62.03, H=4.61, N=6.54. MS: $M^+-1=423.0$ Da.

Example 31: **4-(2,6-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{21}H_{18}N_2O_3S_2$): calculated: C=61.44, H=4.42, N=6.82; found: C=61.01, H=4.27, N=6.70. MS: $M^+-1=409.0$ Da.

20 Example 32: **4-(3,5-Di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. 1H NMR ($DMSO-d_6$) δ 1.20 (s, 18H), 4.90 (s, 2H), 5.15 (s, 2H), 7.11-7.27 (m, 6H), 7.50 (s, 1H), 13.71 (bs, 1H). MS: $M^+-1=494.1$ Da.

25 Example 33: **4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title product was synthesized in a manner analogous to Example 19. 1H NMR ($DMSO-d_6$) δ 2.47

(s, 3H), 2.62-3.31 (m, 4H), 3.53 (bs, 2H), 4.85 (s, 2H), 5.15 (s, 2H), 7.07-7.13 (m, 4H), 7.28 (bs, 4H). MS: $M^+-1=494.1$ Da.

Example 34: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-phenyl-propyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{21}H_{18}N_2O_3S_2$):

5 calculated: C=61.44, H=4.42, N=6.82; found: C=61.35, H=4.24, N=6.62. MS: $M^+-1=410.0$ Da.

Example 35: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[4-(4-phenyl-piperazin-1-ylmethyl)-benzyl]-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. Microanalysis

10 ($C_{30}H_{28}N_4O_3S_2$): calculated: C=64.73, H=5.07, N=10.06; found: C=64.05, H=4.91, N=10.00. MS: $M^+-1=556.1$ Da.

Example 36: **4-(4-*tert*-Butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{23}H_{22}N_2O_3S_2$):

15 calculated: C=62.99, H=5.06, N=6.39; found: C=62.88, H=4.90, N=6.21. MS: $M^+-1=437.0$ Da.

Example 37: **(S)-4-(3,5-Di-*tert*-butyl-benzyl)-2-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 18. 1H NMR (DMSO- d_6) δ

20 1.20 (s, 18H), 1.50 (d, 3H), 5.02-5.20 (m, 3H), 7.07 (s, 2H), 7.16-7.25 (m, 4H), 7.52 (s, 1H). MS: $M^+-1=508.1$ Da.

Intermediate 22: **4-Biphenyl-3-ylmethyl-3-oxo-3,4-dihydro-2H-1,4-**

benzoxazine-6-carbaldehyde. To a room temperature solution of intermediate 3 in *N,N*-dimethylformamide (30 mL) was added 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) on polystyrene resin

25 (2.69 g, 5.92 mmol, 2.2 mole/g) followed by 3-phenylbenzyl bromide (0.767 g, 3.10 mmol). The reaction was stirred for 3 hours. The resin was then filtered off, and the reaction was washed with dichloromethane. The solution was concentrated under reduced pressure to yield the crude oil. Purification of the

residue by silica gel flash chromatography (25% ethyl acetate/hexane) afforded the title compound as an oil. ¹H NMR (DMSO-d₆) δ 4.96 (s, 2H), 5.27 (s, 2H), 7.19-7.63 (m, 12H), 9.78 (s, 1H). MS: M⁺+1=343.1 Da.

5 Example 38: **4-Biphenyl-3-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 22. Microanalysis (C₂₅H₁₈N₂O₃S₂): calculated: C=65.48, H=3.96, N=6.11; found: C=65.37, H=4.01, N=6.20. MS: M⁺-1=458.0 Da.

10 Example 39: **4-(3,5-Dimethyl-4-morpholin-4-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19, using 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene resin as in Example 38, instead of cesium carbonate. ¹H NMR (DMSO-d₆) δ 2.26 (s, 6H), 2.47-2.51 (m, 2H), 2.98-3.37 (m, 2H), 3.44-3.55 (m, 6H), 4.75 (s, 2H), 5.19 (s, 2H), 6.89 (d, 1H), 6.96 (s, 2H), 7.12-7.21 (m, 3H). MS: 15 M⁺-1=509.1 Da.

Example 40: **4-(3-Iodo-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 4.91 (s, 2H), 5.14 20 (s, 2H), 7.13-7.16 (m, 2H), 7.23 (d, 1H), 7.31 (d, 1H), 7.49 (s, 1H), 7.62 (d, 2H), 7.72 (s, 1H). MS: M⁺-1=507.9 Da.

Example 41: **4-(3-Bromo-5-iodo-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 4.93 (s, 2H), 5.13 25 (s, 2H), 7.08 (s, 1H), 7.25 (dd, 2H), 7.52 (d, 1H), 7.71 (s, 1H), 7.84 (s, 1H). MS: M⁺-1=587.8 Da.

Example 42: **4-(3-Methyl-5-morpholin-4-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMSO-d₆) δ 2.26 (s, 3H), 2.46 (bs, 6H), 3.52 (bs, 4H), 3.61 (s, 2H), 4.89 (s, 2H), 5.14 (s, 2H), 7.00-7.12 (m, 5H), 7.21 (d, 1H), 7.33 (s, 1H). MS: M⁺+1=495.1 Da.

Example 43: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-1,1',3',1''-terphenyl-5'-ylmethyl-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 4.94 (s, 2H), 5.29 (s, 2H), 7.11-7.74 (m, 14H).

Example 44: **Trifluoro-methanesulfonic acid 3-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-5-trifluoromethanesulfonyloxy-phenyl ester**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis (C₂₁H₁₂F₆N₂O₉S₄): calculated: C=37.17, H=1.78, N=4.13; found: C=36.73, H=1.64, N=4.04. MS: M⁺-1=676.9 Da.

Example 45: **4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis (C₂₆H₂₉N₃O₃S₂): calculated: C=63.00, H=5.90, N=8.48; found: C=62.85, H=4.84, N=7.71. MS: M⁺-1=495.1 Da.

Intermediate 23: **(2-Fluoro-4-formyl-6-nitro-phenoxy)-acetic acid ethyl ester**. 3-fluoro-4-hydroxy-5-nitro-benzaldehyde was synthesized in a manner analogous to intermediate 11 by using 3-fluoro-4-hydroxy-benzaldehyde instead of 4-hydroxy-2,5-dimethylbenzaldehyde. The title compound was synthesized in a manner analogous to intermediate 7 using 3-fluoro-4-hydroxy-5-nitro-benzaldehyde instead of 5-nitrovanillin. MS: M⁺+1=268.2 Da.

Intermediate 24: **8-Fluoro-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. Intermediate 23 was reacted to form 8-fluoro-6-hydroxymethyl-

4*H*-benzo[1,4]oxazin-3-one in an analogous manner to intermediate 3. ¹H NMR (DMSO-*d*₆) δ 4.34 (s, 2H), 4.59 (s, 2H), 6.66 (s, 1H), 6.74 (s, 1H), 6.7 (s, 1H), 10.86 (bs, 1H). To a solution of 8-fluoro-6-hydroxymethyl-4*H*-benzo[1,4]oxazin-3-one (4.75 g, 24.09 mmol) in dichloromethane (250 mL) at room temperature was added 4-methylmorpholine-*N*-oxide (4.23 g, 36.1 mmol), TPAP (tetrapropylammonium perruthenate) (0.042 g, 1.2 mmol), and 4A molecular sieves (0.500 g). The reaction was stirred for overnight. The reaction mixture was then filtered through a pad of celite. The celite cake was washed with dichloromethane (100 mL). The solution was then concentrated under reduced pressure to yield a dark oil. This solution was then filtered through SiO₂ and washed with ethyl acetate to remove final traces of the TPAP catalyst to yield the title compound. MS: M⁺-1=194.1 Da.

Example 46: 4-Benzyl-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one. The title compound was synthesized in a manner analogous to Example 38 using intermediate 24. ¹H NMR (DMSO-*d*₆) δ 4.97 (s, 2H), 5.15 (s, 2H), 6.87 (s, 1H), 7.20-7.29 (m, 6H), 7.38 (s, 1H). MS: M⁺-1=400.1 Da.

Intermediate 25: (2-Chloro-4-formyl-6-nitro-phenoxy)-acetic acid ethyl ester. 3-Chloro-4-hydroxy-5-nitro-benzaldehyde was synthesized in a manner analogous to intermediate 11 by using 3-chloro-4-hydroxybenzaldehyde instead of 4-hydroxy-2,5-dimethylbenzaldehyde. The title compound was synthesized in a manner analogous to intermediate 7 using (2-chloro-4-formyl-6-nitro-phenoxy)-acetic acid ethyl ester instead of 5-nitrovanillin. Microanalysis (C₁₁H₁₀Cl₁N₁O₆): calculated: C=45.93, H=3.50, N=4.87; found: C=46.07, H=3.52, N=4.85.

Intermediate 26: 8-Chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbaldehyde. The title compound was synthesized in a manner analogous to intermediate 2 and intermediate 3 using intermediate 25. MS: M⁺-1=210.1 Da.

Example 47: **8-Chloro-4-(3,5-di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38 using intermediate 26.

¹H NMR (DMF-d₇) δ 1.24 (s, 18H), 5.14 (s, 2H), 5.30 (s, 2H), 7.14 (s, 1H), 7.24 (s, 2H), 7.36 (s, 1H), 7.46 (s, 1H), 7.51 (s, 1H). MS: M⁺-1=528.2 Da.

Example 48: **4-[3-(4-Methyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMSO-d₆) δ 2.62 (m, 3H), 2.74-3.30 (m, 8H), 3.57 (bs, 2H), 4.84 (s, 2H), 5.14 (s, 2H), 7.03-7.17 (m, 6H), 7.26 (t, 1H), 7.35 (s, 1H). MS: M⁺-1=494.2 Da.

Example 49: **8-Chloro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 47. Microanalysis (C₁₂H₇Cl₁N₂O₃S₂): calculated: C=44.11, H=2.16, N=8.57; found: C=44.20, H=2.04, N=7.56. MS: M⁺-1=325.0 Da.

Example 50: **4-Benzyl-8-chloro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 47. Microanalysis (C₁₉H₁₃Cl₁N₂O₃S₂): calculated: C=54.74, H=3.14, N=6.72; found: C=54.64, H=3.62, N=5.70. MS: M⁺-1=416.1 Da.

Example 51: **4-(3,5-Di-*tert*-butyl-benzyl)-8-methoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 6 using BEMP resin as in intermediate 22. Microanalysis (C₂₈H₃₂N₂O₄S₂): calculated: C=64.10, H=6.15, N=5.34; found: C=63.64, H=5.79, N=4.88. MS: M⁺-1=524.2 Da.

Example 52: **4-(3-*tert*-Butyl-5-iodo-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 1.20 (s, 18H),

4.90 (s, 2H), 5.12 (s, 2H), 7.10 (s, 1H), 7.20 (dd, 2H), 7.36 (s, 1H), 7.41 (s, 1H), 7.48 (s, 1H), 7.55 (s, 1H). MS: $M^+ - 1 = 564.0$ Da.

Example 53: **8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 24. ^1H NMR (DMSO- d_6) δ 4.70 (s, 2H), 6.87 (s, 2H), 7.24 (d, 1H), 7.45 (s, 1H). MS: $M^+ - 1 = 309.0$ Da.

Example 54: **4-(3,5-Di-*tert*-butyl-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($\text{C}_{27}\text{H}_{29}\text{F}_1\text{N}_2\text{O}_3\text{S}_2$): calculated: C=63.26, H=5.70, N=5.46; found: C=62.96, H=5.74, N=5.40. MS: $M^+ - 1 = 512.2$ Da.

Intermediate 27: **4-(3-*tert*-Butyl-5-iodo-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 22 using intermediate 3 and 1-bromomethyl-3-*tert*-butyl-5-iodo-benzene. MS: $M^+ - 1 = 449.0$ Da.

Intermediate 28: **3-*tert*-Butyl-5-(6-formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-benzonitrile**. To a *N,N*-dimethylformamide (10 mL) solution of intermediate 27 (0.500 g, 1.11 mmol) was added zinc cyanide (0.078 g, 0.66 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.051 g, 0.04 mmol). The reaction was heated to 80°C for 5.5 hours. The reaction was cooled to room temperature, filtered through a pad of celite, and diluted with ethyl acetate. The organic layer was washed with 10% ammonium hydroxide (1 \times 20 mL) and brine (1 \times 20 mL). The organic layer was dried over MgSO_4 , filtered and then concentrated under reduced pressure to yield a crude oil. This material was chromatographed using 20% ethyl acetate/hexane to yield the title compound MS: $M^+ - 1 = 348.2$ Da.

Example 55: **3-*tert*-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzonitrile**. The title

compound was synthesized in a manner analogous to Example 1 using intermediate 28. Microanalysis ($C_{24}H_{21}N_3O_3S_2$): calculated: C=62.18, H=4.57, N=9.06; found: C=61.64, H=4.73, N=8.99. MS: $M^+-1=463.1$ Da.

5 Intermediate 29: **4-(3-*tert*-Butyl-5-vinyl-benzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbaldehyde**. To a toluene solution of intermediate 27 (0.500 g, 1.11 mmol) was added vinyl tributyl tin (0.387 g, 1.22 mmol) followed by bis-triphenylphosphine palladium dichloride (0.031 g, 0.04 mmol). The reaction was heated to reflux for 5 hours. This material was chromatographed using 25% ethyl acetate/hexane to yield the title compound as a solid. MS: $M^+-1=349.2$ Da.

10 Example 56: **4-(3-*tert*-Butyl-5-vinyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 29. Microanalysis ($C_{25}H_{24}N_2O_3S_2$): calculated: C=64.63, H=5.21, N=6.03; found: C=64.41, H=5.07, N=5.64. MS: $M^+-1=464.1$ Da.

15 Example 57: **3-*tert*-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoic acid methyl ester**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis ($C_{25}H_{24}N_2O_5S_2$): calculated: C=60.47, H=4.87, N=5.64; found: C=60.29, H=4.97, N=5.60. MS: $M^+-1=496.1$ Da.

20 Intermediate 30: **3-*tert*-Butyl-5-(6-formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-benzoic acid methyl ester**. The title compound was synthesized in a manner analogous to intermediate 22 using intermediate 3 and 3-bromomethyl-5-*tert*-butyl-benzoic acid methyl ester. MS: $M^+-1=381.3$ Da.

25 Intermediate 31: **3-*tert*-Butyl-5-(6-formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-benzoic acid**. The title compound was synthesized in a manner analogous to intermediate 23 using intermediate 30. MS: $M^+-1=367.2$ Da.

Example 58: **3-*tert*-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoic acid**. The

title compound was synthesized in a manner analogous to Example 1 using intermediate 31. ¹H NMR (DMSO-d₆) δ 1.25 (s, 9H), 4.85 (s, 2H), 5.21 (s, 2H), 7.08-7.20 (m, 4H), 7.53 (s, 1H), 7.70 (s, 1H), 7.79 (s, 1H). MS: M⁺-1=482.1 Da.

Intermediate 32: **[3-*tert*-Butyl-5-(6-formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-benzoylamino]-acetic acid *tert*-butyl ester**. To a 0°C

5 tetrahydrofuran (50 mL) solution of intermediate 31 (0.172 g, 0.47 mmol) was added L-alanine *tert*-butyl ester hydrochloride (0.078 g, 0.47 mmol), 4-methylmorpholine (0.11 mL, 1.17 mmol), 1-hydroxybenzotriazole (0.094 g, 0.702 mmol), and 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
10 (0.13 g, 0.70 mmol). The reaction was allowed to warm slowly to room temperature and then stirred overnight. The reaction was then diluted with ethyl acetate (150 mL). The organic layer was washed in succession with 5% citric acid (2 × 50 mL), saturated sodium bicarbonate (2 × 50 mL), and brine (1 × 50 mL). The organic layer was dried over MgSO₄, filtered and then concentrated under
15 reduced pressure to yield the title compound. MS: M⁺-1=480.2 Da.

Example 59: **{3-*tert*-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoylamino}-acetic acid *tert*-butyl ester**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 32. ¹H NMR (DMSO-d₆) δ 1.28 (s, 9H), 1.35
20 (s, 9H), 3.80 (d, 2H), 4.90 (s, 2H), 5.22 (s, 2H), 7.13-7.23 (m, 3H), 7.39 (s, 1H), 7.49 (s, 1H), 7.64 (s, 1H), 7.75 (s, 1H), 7.80 (t, 1H). MS: M⁺-1=595.2 Da.

Example 60: **{3-*tert*-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzoylamino}-acetic acid**. The title compound was synthesized in a manner analogous to intermediate
25 6 using Example 59. ¹H NMR (DMSO-d₆) δ 1.27 (s, 18H), 3.82 (d, 2H), 4.91 (s, 2H), 5.22 (s, 2H), 7.13-7.23 (m, 3H), 7.41 (s, 1H), 7.49 (s, 1H), 7.64 (s, 1H), 7.76 (s, 1H), 8.79 (t, 1H), 13.70 (bs, 1H). MS: M⁺-1=539.1 Da.

Example 61: **4-(3,5-Di-*tert*-butyl-benzyl)-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 35 using BEMP resin as in intermediate 22. Microanalysis (C₂₈H₃₂N₂O₃S₂): calculated: C=66.11, H=6.34, N=5.51; found: C=66.13, H=6.32, N=5.21. MS: M⁺-1=507.3 Da.

Example 62: **4-[1-(3,5-Di-*tert*-butyl-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis (C₂₈H₃₂N₂O₃S₂): calculated: C=66.11, H=6.34, N=5.51; found: C=65.69, H=6.25, N=5.39. MS: M⁺-1=508.3 Da.

Intermediate 33: **4-(3-*tert*-Butyl-5-ethyl-benzyl)-6-hydroxymethyl-4*H*-benzo[1,4]oxazin-3-one**. To a methanol solution (50 mL) solution of intermediate 29 (0.16 g, 0.45 mmol) was added platinum oxide (0.025 g). The solution was then pressurized with hydrogen for 36 hours. The reaction was then filtered through a pad of celite and washed with methanol. The methanol solution was concentrated under reduced pressure to yield the title compound. MS: M⁺-1=351.2 Da.

Intermediate 34: **4-(3-*tert*-Butyl-5-ethyl-benzyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbaldehyde**. Intermediate 33 was oxidized to the title compound using TPAP in a manner analogous to that described for intermediate 24. MS: M⁺-1=351.3 Da.

Example 63: **4-(3-*tert*-Butyl-5-ethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 34. ¹H NMR (DMSO-d₆) δ 1.06 (t, 3H), 1.17 (s, 9H), 2.48 (q, 2H), 4.87 (s, 2H), 5.10 (s, 2H), 6.85 (s, 1H), 7.05-7.21 (m, 5H), 7.45 (s, 1H). MS: M⁺-1=465.2 Da.

Example 64: **4-(3-Acetyl-5-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized

in a manner analogous to Example 56. ¹H NMR (DMSO-d₆) δ 1.26 (s, 9H), 2.53 (s, 3H), 4.94 (s, 2H), 5.26 (s, 2H), 7.15-7.26 (m, 3H), 7.51 (s, 1H), 7.63 (d, 2H), 7.81 (s, 1H). MS: M⁺-1=480.2 Da.

5 Example 65: **4-(5-*tert*-Butyl-biphenyl-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 56. ¹H NMR (DMSO-d₆) δ 1.29 (s, 9H), 4.94 (s, 2H), 5.24 (s, 2H), 7.14-7.56 (m, 12H). MS: M⁺-1=514.2 Da.

10 Example 66: **5-[4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 38 using thiazoladinedione instead of rhodanine. ¹H NMR (DMSO-d₆) δ 1.23 (s, 18H), 4.92 (s, 2H), 5.16 (s, 2H), 7.06 (s, 3H), 7.15-7.27 (m, 2H), 7.65 (s, 1H). MS: M⁺-1=478.3 Da.

15 Example 67: **8-Chloro-4-(3,5-dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 47. ¹H NMR (DMSO-d₆) δ 2.22 (s, 6H), 5.04 (s, 2H), 5.08 (s, 2H), 6.87 (s, 2H), 6.90 (s, 2H), 7.42 (s, 1H), 7.47 (s, 1H). MS: M⁺-1=443.2 Da.

20 Example 68: **5-[8-Chloro-4-(3,5-dimethyl-benzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 47 using thiazoladinedione instead of rhodanine. ¹H NMR (DMSO-d₆) δ 2.20 (s, 6H), 5.03 (s, 2H), 5.07 (s, 2H), 6.89 (t, 3H), 7.44 (s, 1H), 7.58 (s, 1H). MS: M⁺-1=427.2 Da.

25 Example 69: **4-(3,5-Dimethyl-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis (C₂₁H₁₇F₁N₂O₃S₂): calculated: C=58.86, H=4.00, N=6.54; found: C=58.98, H=3.97, N=6.51. MS: M⁺-1=427.2 Da.

Intermediate 35: **4-(3-Bromomethyl-5-*tert*-butyl-benzyl)-3-oxo-3,4-dihydro-2H[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 16 using intermediate 3 and 1,3-*bis*-bromomethyl-5-*tert*-benzene. MS: $M^+ + 1 = 416.2$ Da.

5 Intermediate 36: **Acetic acid 3-*tert*-butyl-5-(6-formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzyl ester**. To an acetic acid (10 mL) solution of intermediate 35 (0.567 g, 1.36 mmol) was added silver acetate (0.375 g). The reaction was heated to reflux for 1.5 hours. The reaction was cooled to room temperature, and the precipitate was filtered off and washed with ethyl acetate (15
10 mL). The filtrate was concentrated under reduced pressure to yield a crude oil. This material was chromatographed using 25% ethyl acetate/hexane to yield the title product. MS: $M^+ - 1 = 395.3$ Da.

Example 70: **Acetic acid 3-*tert*-butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzyl ester**. The title
15 compound was synthesized in a manner analogous to Example 66 using intermediate 36. ^1H NMR (DMSO- d_6) δ 1.23 (s, 9H), 1.98 (s, 3H), 4.91 (s, 2H), 4.99 (s, 2H), 5.18 (s, 2H), 7.04 (s, 1H), 7.15-7.25 (m, 4H), 7.36 (s, 1H), 7.50 (s, 1H). MS: $M^+ - 1 = 509.3$ Da.

Example 71: **8-Fluoro-4-(4-morpholin-4-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound
20 was synthesized in a manner analogous to Example 19 using intermediate 24, 1,4-dibromomethylbenzene, and morpholine. ^1H NMR (DMSO- d_6) δ 2.61 (bs, 4H), 3.59 (bs, 4H), 3.75 (bs, 2H), 4.99 (s, 2H), 5.19 (s, 2H), 6.85 (s, 1H), 7.22 (d, 1H), 7.26 (s, 1H), 7.34 (s, 4H). MS: $M^+ + 1 = 500.1$ Da.

Example 72: **4-(4-Diethylaminomethyl-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound
25 was synthesized in a manner analogous to Example 71. ^1H NMR (DMSO- d_6) δ 1.13-1.16 (m, 6H), 2.85-3.06 (m, 4H), 4.10-4.28 (bs, 2H), 4.97 (s, 2H), 5.21 (s,

2H), 6.80 (s, 1H), 6.99 (s, 1H), 7.13 (dd, 1H), 7.40 (d, 1H), 7.46 (d, 1H). MS: $M^+ + 1 = 86.2$ Da.

5 Example 73: **8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-piperidin-1-ylmethyl-benzyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 71. ^1H NMR (DMSO- d_6) δ 1.25-1.80 (m, 6H), 2.75-3.05 (m, 4H), 4.14 (bs, 2H), 4.96 (s, 2H), 5.21 (s, 2H), 6.80 (s, 1H), 7.00 (s, 1H), 7.14 (d, 1H), 7.39-7.45 (m, 4H). MS: $M^+ + 1 = 498.1$ Da.

10 Example 74: **4-{4-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzyl}-piperazine-1-carboxylic acid *tert*-butyl ester**. The title compound was synthesized in a manner analogous to Example 19. ^1H NMR (DMSO- d_6) δ 1.36 (s, 9H), 2.45 (bs, 4H), 3.31 (bs, 4H), 3.63 (s, 2H), 4.91 (s, 2H), 5.17 (s, 2H), 7.07 (d, 1H), 7.14 (d, 1H), 7.31 (dd, 1H), 7.31 (s, 4H), 7.39 (s, 1H). MS: $M^+ + 1 = 581.2$ Da.

15 Example 75: **4-{4-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzyl}-piperazine-1-carboxylic acid *tert*-butyl ester**. The title compound was synthesized in a manner analogous to Example 19 using thiazoladinedione instead of rhodanine. ^1H NMR (DMSO- d_6) δ 1.35 (s, 9H), 2.28-2.30 (m, 4H), 3.26-3.30 (m, 4H), 3.46 (s, 2H), 4.90 (s, 2H), 5.16 (s, 2H), 7.11-7.15 (m, 2H), 7.22-7.27 (m, 5H), 7.61 (s, 1H). MS: 20 $M^+ + 1 = 565.2$ Da.

Example 76: **5-[8-Fluoro-3-oxo-4-(4-piperidin-1-ylmethyl-benzyl)-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 71, using diethylamine and 1,4-dibromomethylbenzene, and substituting thiazoladinedione for rhodanine. ^1H NMR (DMSO- d_6) δ 1.42 (bs, 2H), 1.58 (bs, 4H), 2.78 (bs, 4H), 3.94 (bs, 2H), 4.97 (s, 2H), 5.19 (s, 2H), 6.90 (s, 1H), 7.17 (d, 1H), 7.30 (s, 1H), 7.34-7.40 (m, 4H). MS: $M^+ + 1 = 482.1$ Da.

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Example 77: **4-[4-(4-Butyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMF-d₇) δ 0.87 (t, 3H), 1.26-1.35 (m, 2H), 1.53-1.61 (m, 2H), 2.60-2.95 (m 4H), 3.58 (s, 2H), 4.94 (s, 2H), 5.29 (s, 2H), 7.12-7.22 (m, 4H), 7.32 (d, 2H), 7.39 (d, 2H). MS: M⁺+1=537.2 Da.

Intermediate 37: **4-(4-Bromomethyl-benzyl)-8-chloro-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 16 using intermediate 26 and 1,4-dibromomethylbenzene.

Intermediate 38: **8-Chloro-4-(4-dimethylaminomethyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 17 using intermediate 37 and dimethylamine.

Example 78: **8-Chloro-4-(4-diethylaminomethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 38. ¹H NMR (DMSO-d₆) δ 1.15 (t, 6H), 2.98 (bs, 4H), 4.19 (bs, 2H), 5.01 (s, 2H), 5.21 (s, 2H), 6.92 (s, 1H), 6.98 (s, 1H), 7.28 (s, 1H), 7.40 (d, 2H), 7.46 (d, 2H). MS: M⁺+1=502.1 Da.

Example 79: **8-Chloro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-piperidin-1-ylmethyl-benzyl)-4H-1,4-benzoxazin-3-one; compound with toluene-4-sulfonic acid**. The title compound was synthesized in a manner analogous to Example 78 using piperidine instead of dimethylamine. To a suspension of crude product in benzene was added *p*-toluenesulfonic acid monohydrate (0.190 g, 1.05 equiv) and mixture heated to reflux for 18 hours. The reaction was concentrated to a yellow residue that was dissolved in CH₂Cl₂ with heat. Upon cooling a yellow precipitate resulted which was filtered and dried. ¹H NMR (DMSO-d₆) δ 1.25-1.40 (m, 1H), 1.50-1.70 (m, 3H), 1.75-1.80 (m, 2H),

2.27 (s, 3H), 2.78-2.90 (m, 2H), 3.25-3.35 (m, 2H), 4.26 (bs, 2H), 5.08 (s, 2H), 5.24 (bs, 2H), 6.89 (s, 1H), 7.09 (d, 2H), 7.40-7.52 (m, 4H), 9.14 (bs, 1H). MS: $M^+ + 1 = 514.1$ Da.

Example 80: **8-Chloro-4-(4-morpholin-4-ylmethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 78 using morpholine instead of dimethylamine. ^1H NMR (DMSO- d_6) δ 2.64 (bs, 4H), 3.30 (bs, 4H), 3.78 (bs, 2H), 5.03 (s, 2H), 5.19 (s, 2H), 6.94 (s, 1H), 7.27-7.38 (m, 7H). MS: $M^+ + 1 = 516.0$ Da.

Intermediate 39: **4-Formyl-2-nitrophenylsulfanyl acetic acid**. In acetonitrile (150 mL) was stirred 4-chloro-3-nitrobenzaldehyde (7.42 g, 40 mmol), thioglycolic acid (4.6 g, 50 mmol), and triethylamine (1.01 g, 100 mmol). The mixture stirred at room temperature overnight. The mixture was evaporated free of solvent and the residue partitioned between water (200 mL) and ethyl acetate (200 mL). The organic phase was discarded and the aqueous phase made acidic with concentrated HCl. The mixture was allowed to stand overnight to precipitate. The solid was collected by filtration, washed with water (2×200 mL) and then dried in vacuo at 65°C for 3 hours. MS: $M^+ - 1 = 240$.

Intermediate 40: **3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxaldehyde**.

In ammonium hydroxide (20 mL) was suspended the intermediate 39 (1.91 g, 7.91 mmol). To this was added dropwise a solution of iron (II) sulfate heptahydrate (22 g) in water (48 mL). The mixture warmed to 90°C for 1 hour and then filtered through celite to remove the iron salts. The filtrate was treated with 6N HCl and allowed to precipitate. The solid was collected by filtration and warmed to reflux in ethanol (100 mL). The solution was allowed to cool and then filtered to collect the solid. MS: $M^+ + 1 = 194.1$.

Intermediate 41: **4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxaldehyde**. The title compound was synthesized in a manner analogous to Example 19 using intermediate 40. MS: $M^+ + 1 = 84.1$.

Example 81: **4-Benzyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 41. MS: $M^+ + 1 = 399.1$. Microanalysis ($C_{19}H_{14}N_2O_2S_3 \cdot 0.05 H_2O$): calculated: C=57.13, H=3.56, N=7.02, S=24.08, KF(H_2O)=0.23; found: C=56.97, H=3.62, N=6.98, S=23.87, KF(H_2O)=0.25.

Example 82: **4-(3,5-Di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one**. The title compound was synthesized in a manner analogous to Example 81. MS: $M^+ + 1 = 511.1$. Microanalysis ($C_{27}H_{30}N_2O_2S_3 \cdot 0.7 Et_2O$): calculated: C=63.61, H=6.63, N=4.98; found: C=63.65, H=6.93, N=4.61.

Example 83: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one**. The title compound was synthesized in a manner analogous to Example 81. MS: $M^+ + 1 = 309.0$. Microanalysis ($C_{12}H_8N_2O_2S_3 \cdot 0.2 H_2O$): calculated: C=46.19, H=2.72, N=8.98, S=30.83; found: C=46.47, H=2.79, N=8.58, S=30.08.

Example 84: **6-(4-Oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. To 20 mL of anhydrous tetrahydrofuran at $-78^\circ C$ was added dropwise 5.6 mL of $TiCl_4$ (1.0 M in dichloromethane, 5.6 mM). A mixture of intermediate 3 (0.5 g, 2.8 mmol) and 2-thiooxazolid-4-one (0.5 g, 4.9 mmol) was added all at once, and the resulting mixture was stirred. The reaction was allowed to warm to $0^\circ C$ and anhydrous pyridine (0.9 mL, 11.1 mmol) was added to the stirring mixture dropwise. Upon addition of the pyridine, the mixture was warmed to room temperature, then heated to $50^\circ C$ and stirred overnight. The reaction was diluted with water, resulting in a precipitate. The precipitate was collected by filtration and triturated with hot methanol. MS (APCI-): $M^+ - 1 = 275.0$. Microanalysis ($C_{12}H_8N_2O_4S$): found: C=52.07; H=2.92; N=9.84; theory, C=52.17; H=3.02; N=10.14.

Example 85: **5-[4-(3,5-Di-*tert*-butyl-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 2, using cesium carbonate as in intermediate 16, and using thiazolidine dione in place of rhodanine. MS

5 (APCI⁺): M⁺+1= 479.1. Microanalysis (C₂₇H₃₀N₂O₄S): calculated: C=67.76; H=6.32; N=5.85; found: C=67.53; H=6.38; N=5.83.

Example 86: **3-(3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-pyrrolidine-2, 5-dione**. Maleimide (1.0 g, 10.3 mmol) and triphenylphosphine (0.96 g, 9.9 mmol) were stirred in 20 mL of glacial acetic acid. The mixture was heated to 100°C and stirred at this temperature for 0.5 hour. The acetic acid was removed in vacuo and the resulting pink oil was triturated with ether to obtain a solid. The ether was decanted, and the solid was triturated with acetone to give a white solid. The white solid was collected by filtration and dried under vacuum.

10 To a solution of intermediate 3 (0.5 g, 2.8 mmol) in anhydrous methyl sulfoxide was added the solid phosphine from above (0.5 g, 1.4 mmol); the resulting solution was stirred overnight. Another equivalent of phosphine intermediate was added, and the mixture was stirred another 24 hours. The mixture was diluted with water and the resulting brown solid was collected by filtration. The solid was rinsed with water and ether, then dried under vacuum. MS (APCI⁻): M⁺-1=257.1. Microanalysis (C₁₃H₁₀N₂O₄·0.72 H₂O): calculated: C=57.58; H=4.06; N=10.14; found: C=57.57; H=4.25; N=10.33.

Example 87: **5-(3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-imidazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 84, except that hydantoin was substituted for 2-thiooxazolid-4-one. MS (APCI⁻): M⁺-1=258.0. Microanalysis (C₁₂H₉N₃O₄·0.85 H₂O): found: C=52.50; H=3.79; N=15.10; calculated, C=52.50; H=3.93; N=15.31.

Intermediate 42: **(4-Formyl-2-nitro-phenoxy)acetic acid ethyl ester**. To a solution of 4-hydroxy-3-nitrobenzaldehyde (5.00 g, 29.9 mmol) in tetrahydrofuran/DMF (300 mL/120 mL) was added NaH (60%, 1.32 g,

32.9 mmol), followed by ethyl bromoacetate (5.49 g, 3.65 mL, 32.9 mmol). The mixture was heated at reflux for 20 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), acidified to pH 2 with 1N HCl, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), the organic extracts were combined and washed with saturated NaHCO₃ (2 × 50 mL), brine (1 × 50 mL), dried over MgSO₄, and concentrated to an amber oil. Purification of the residue by silica gel flash chromatography (25% ethyl acetate/hexanes) afforded the title compound. ¹H NMR (DMSO-d₆) δ 1.91 (t, J=7.08 Hz, 3H), 4.16 (q, J=7.08 Hz, 2H), 5.15 (s, 2H), 7.50 (d, J=8.79 Hz, 1H), 8.12-8.14 (m, 1H), 8.42 (d, J=1.95 Hz, 1H), 9.93 (s, 1H) ppm. MS: M⁺-1=252.1 Da.

Intermediate 43: **4-Hydroxy-6-hydroxymethyl-4H-benzo[1,4]oxazin-3-one**. To a solution of NaBH₄ (1.00 g, 26.4 mmol) in H₂O (10 mL) was carefully added a suspension of Pd/C (10%, 0.200 g, 0.187 mmol) in H₂O (10 mL). The suspension was diluted with 20 mL of dioxane and saturated with N₂ gas for 5 minutes. A solution of intermediate 42 (1.00 g, 3.74 mmol) in dioxane (20 mL) was added dropwise over 15 minutes, while N₂ was bubbled through the mixture. After the addition was complete, the reaction was continued for 25 minutes with N₂ bubbling through. The mixture was then filtered through a pad of celite, the filtrate was acidified with 10% HCl, diluted with 100 mL of H₂O, and the organic solvent was removed under reduced pressure, resulting a solid precipitate. The pure solid was isolated by filtration. ¹H NMR (DMSO-d₆) δ 4.43 (dd, J=5.62, 2.44 Hz, 2H), 4.71 (d, J=2.93 Hz, 2H), 5.16-5.20 (m, 1H), 6.90 (s, 2H), 7.20 (s, 1H) ppm. MS: M⁺-1=194.2 Da.

Intermediate 44: **4-(3,4-Dichloro-benzyloxy)-6-hydroxymethyl-4H-benzo[1,4]oxazin-3-one**. To a mixture of intermediate 43 (0.200 g, 1.03 mmol) in 10 mL of acetone were added K₂CO₃ (0.283 g, 2.05 mmol), and 3,4-dichlorobenzylbromide (0.270 g, 1.13 mmol). The mixture was heated at reflux for 2 hours, cooled to room temperature, and H₂O (5 mL) and 1N HCl (5 mL)

were added. The organic solvents were removed under reduced pressure, and the residue was stirred with ethyl acetate (20 mL) and 1N HCl (10 mL). A white precipitate was isolated by filtration and dried in vacuo to provide the title compound. ¹H NMR (DMSO-d₆) δ 4.44 (d, J=5.13 Hz, 2H), 4.74 (s, 2H), 5.09 (s, 2H), 5.19–5.21 (m, 1H), 6.95 (s, 2H), 7.14 (s, 1H), 7.53 (d, J=8.30 Hz, 1H), 7.67 (d, J=8.06 Hz, 1H), 7.83 (s, 1H) ppm. MS: M⁺+1=336.0 Da.

Intermediate 45: **4-(3,4-Dichloro-benzyloxy)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. Intermediate 44 was reduced to the title compound using TPAP in a manner analogous to that described for intermediate 24. ¹H NMR (DMSO-d₆) δ 4.93 (s, 2H), 5.15 (s, 2H), 7.19 (d, J=8.79 Hz, 1H), 7.54–7.56 (m, 1H), 7.60–7.62 (m, 2H), 7.67 (d, J=8.06 Hz, 1H), 7.85 (d, J=1.47 Hz, 1H), 9.90 (s, 1H) ppm. MS: M⁺+1=352.0 Da.

Example 88: **4-(3,4-Dichloro-benzyloxy)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 45. MP>300°C. MS: M⁺-1=465.0 Da.

Example 89: **4-(3,5-Dimethyl-benzyloxy)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 88. MP>300°C. MS: M⁺+1=427.1 Da.

Intermediate 46: **(4-Bromo-2-nitro-phenoxy)-acetic acid ethyl ester**. The title compound was prepared in a manner analogous to intermediate 42 from 4-bromo-2-nitrophenol. ¹H NMR (DMSO-d₆) δ 1.18 (t, J=7.08 Hz, 3H), 4.14 (q, J=7.08 Hz, 2H), 5.02 (s, 2H), 7.27 (d, J=9.03 Hz, 1H), 7.78–7.81 (m, 1H), 8.12 (d, J=2.44 Hz, 1H) ppm. MS: M⁺-C₂H₅=288.0 Da.

Intermediate 47: **6-Bromo-4-hydroxy-4H-benzo[1,4]oxazin-3-one**. The title compound was prepared in a manner analogous to intermediate 43 from intermediate 46. MP=201–204°C. MS: M⁺-1=243.9 Da.

Intermediate 48: **4-Benzyloxy-6-bromo-4H-benzo[1,4]oxazin-3-one**. The title compound was prepared in a manner analogous to intermediate 43 from intermediate 47 (0.500 g, 2.05 mmol) and purified by silica gel flash column chromatography (10% ethyl acetate/hexanes). ¹H NMR (DMSO-d₆) δ 4.81 (s, 2H), 5.10 (s, 2H), 6.95 (d, J=3.91 Hz, 1H), 7.14 (d, J=2.44 Hz, 1H), 7.17 (s, 1H), 7.38-7.42 (m, 3H), 7.51 (d, J=1.95 Hz, 1H), 7.53 (d, J=2.93 Hz, 1H) ppm. MS: M⁺-1=334.0 Da.

Intermediate 49: **4-Benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. To a 3-neck 50 mL round bottom flask equipped with a reflux condenser and glass gas inlet tube was added PdCl₂(PPh₃)₂ (10.5 mg, 0.150 mmol), intermediate 48 (0.250 g, 0.748 mmol), and sodium formate (0.101 g, 1.50 mmol). The atmosphere was replaced with carbon monoxide, 2 mL of DMF was added via syringe, and a slow stream of carbon monoxide was bubbled into the vigorously stirred suspension as it was heated to 110°C for 3.5 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (20 mL), and saturated NaHCO₃ (20 mL). The mixture was filtered through a pad of celite. The layers of the filtrate were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL), brine (1 × 10 mL), dried over MgSO₄, filtered and concentrated. ¹H NMR (DMSO-d₆) δ 4.94 (s, 2H), 5.13 (s, 2H), 7.19 (d, J=8.79 Hz, 1H), 7.40-7.42 (m, 3H), 7.54-7.55 (m, 2H), 7.59-7.61 (m, 2H), 9.89 (s, 1H) ppm. MS: M⁺-1=282.1 Da.

Example 90: **4-Benzyloxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 49. MP>300°C. MS: M⁺-1=397.1 Da.

Example 91: **8-Methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-piperidin-1-ylmethyl-benzyl)-4H-benzo[1,4]oxazin-3-one**. The title compound

was prepared in a manner analogous to Example 71 using 1,4-dibromomethyl benzene and piperidine. MP=277-278°C. MS: $M^+-1=493.2$ Da.

5 Example 92: **4-(4-Diethylaminomethyl-benzyl)-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was prepared in a manner analogous to Example 71 using 1,4-dibromomethyl benzene and diethylamine. MP=250-252°C. MS: $M^+-1=481.2$ Da.

10 Example 93: **5-[4-(4-Diethylaminomethyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 19, using thiazoladinedione instead of rhodanine. MP=244-246°C. MS: $M^++1=452.3$ Da.

Example 94: **4-(3,5-Diisopropoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MP=245-247°C. MS: $M^+-1=498.1$ Da.

15 Example 95: **4-(5-tert-Butyl-2-methoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MP=255-257°C. MS: $M^+-1=468.0$ Da.

Example 96: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(2,3,5,6-tetramethyl-benzyl)-4H-1,4-benzoxazin-3-one**. MP=277-280°C. MS: $M^+-1=438.0$ Da.

20 Example 97: **4-(3,4-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MP>300°C. MS: $M^+-1=410.0$ Da.

Example 98: **4-(2,3-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MP>300°C. MS: $M^+-1=410.0$ Da.

25 Example 99: **4-(2,5-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MP>300°C. MS: $M^+-1=410.0$ Da.

Example 100: **4-(2,4-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. ¹H NMR (DMSO-d₆) δ 2.22 (s, 3H), 2.35 (s, 3H), 4.94 (s, 2H), 5.05 (s, 2H), 6.79 (d, J=7.81 Hz, 1H), 6.87 (s, 2H), 7.06 (s, 1H), 7.16 (d, J=8.30 Hz, 1H), 7.25 (dd, J=8.55, 1.71 Hz, 1H), 7.47 (s, 1H), 13.69 (bs, 1H) ppm. MS: M⁺-1=410.0 Da.

Example 101: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-*m*-tolyl-ethyl]-4H-benzo[1,4]oxazin-3-one**. ¹H NMR (DMSO-d₆) δ (s,3H) 2.26-2.83 (t, 2H), 4.089 (t, 2H), 4.71 (s, 2H), 7.00-7.05 (d, 1H), 7.15-7.16 (d, 1H), 7.18-7.20 (m, 4H), 7.44 (s, 1H), 7.69 (s, 1H) ppm. MS: M⁺+1=411 Da.

Example 102: **4-[2-(4-Bromo-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: M⁺+1=475 Da. MP = 274-276°C.

Example 103: **4-[2-(3,4-Dichloro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: M⁺+1=464 Da. MP = 267-269°C.

Example 104: **6-(Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-(4-trifluoromethyl-phenyl)-ethyl]-4H-benzo[1,4]oxazin-3-one**. MS: M⁺+1=465 Da. MP = 253-255°C.

Example 105: **4-[2-(2,4-Dichloro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: M⁺+1=464 Da. MP = 267-269°C.

Example 106: **6-(Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-(3-trifluoromethyl-phenyl)-ethyl]-4H-benzo[1,4]oxazin-3-one**. MS: M⁺+1=465 Da. MP = 241-243°C.

Example 107: **8-Chloro-6-(oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-(4-trifluoromethyl-phenyl)-ethyl]-4H-benzo[1,4]oxazin-3-one**. The title

compound was synthesized in a manner analogous to Example 47. MS:

$M^{+}+1=499$ Da. MP = 275-277°C.

Example 108: **6-(Oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4-[2-(2-trifluoromethyl-phenyl)-ethyl]-4*H*-benzo[1,4]oxazin-3-one**. MS: $M^{+}+1=465$ Da. MP = 283-286°C.

Example 109: **(*S*)-4-[2-(3,4-Dichloro-phenyl)-ethyl]-2-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 18. ¹H NMR (DMSO-*d*₆) δ 1.35-1.37 (d, 3H), 2.89 (t, 3H), 4.05-4.20 (m, 2H), 4.70-4.80 (m, 1H), 7.19-7.21 (m, 3H), 7.40-7.60 (m, 3H), 7.70 (s, 1H) ppm. MS: $M^{+}+1=478$ Da.

Example 110: **8-Chloro-4-[2-(3,4-dichloro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 47. ¹H NMR (DMSO-*d*₆) δ 2.88 (t, 2H), 4.05-4.20 (t, 2H), 4.81 (s, 2H), 7.19-7.21 (d, 2H), 7.30 (s, 1H), 7.41 (s, 1H), 7.50-7.52 (d, 1H), 7.56 (s, 1H), 7.64 (s, 1H) ppm. MS: $M^{+}+1=500$ Da.

Example 111: **4-[2-(3,4-dichloro-phenyl)-ethyl]-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-*d*₆) δ 2.88 (t, 2H), 4.12-4.16 (m, 2H), 4.78 (s, 2H), 7.19-7.21 (m, 1H), 7.31 (s, 1H), 7.47-7.49 (d, 1H), 7.56 (s, 1H), 7.65 (s, 1H) ppm. MS: $M^{+}+1=482$ Da.

Example 112: **4-[2-(3,4-dichloro-phenyl)-ethyl]-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 35. ¹H NMR (DMSO-*d*₆) δ 2.21 (s, 3H), 2.87 (t, 2H), 4.12 (t, 2H), 4.79-4.81 (s, 2H), 7.06 (s, 1H), 7.19-7.21 (d, 1H), 7.38 (s, 1H), 7.48-7.58 (m, 1H), 7.64 (s, 1H) ppm. MS: $M^{+}+1=478$ Da.

Example 113: **4-[2-(Bis-trifluoromethyl-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: $M^{+}+1=531$ Da. MP = 261-263°C.

Intermediate 50: **3-Oxo-4-(3-pyridin-4-yl-benzyl)-3,4-dihydro-2H-**

5 **benzo[1,4]oxazine-6-carbaldehyde**. To a solution of 4-(3-iodo-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde (0.100 g, 0.254 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.015 g, 0.01 mmol) in DMF (20.0 mL) was added pyridine-4-boronic acid (0.034 g, 0.279 mmol) followed by the addition of Na_2CO_3 (2 mL, 2.0 M solution). The solution was heated to reflux overnight with good stirring. The
10 heat was turned off, the solution was poured into H_2O (30 mL), and the organic phase was extracted with CH_2Cl_2 (3×40 mL). The organic phase was then dried over MgSO_4 , filtered, and concentrated down under reduced pressure. The product was chromatographed with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1).

Example 114: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-pyridin-4-yl-benzyl)-4H-benzo[1,4]-oxazin-3-one**. The title compound was synthesized in
15 a manner analogous to Example 1 from intermediate 50. MS: $M^{+}+1=460$ Da. MP = 297-299°C.

Intermediate 51: **4-(3-Iodo-5-methyl-benzyl)-3-oxo-3,4-dihydro-2H-**

20 **benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 4 using intermediate 3 and 1-bromomethyl-3-iodo-5-methyl-benzene. ^1H NMR ($\text{DMSO}-d_6$) δ 2.20 (s, 3H), 4.95 (s, 2H), 5.15 (s, 2H), 7.10 (s, 1H), 7.19-7.21, (d, 1H), 7.43-7.47 (m, 3H), 7.58-7.59 (d, 1H) ppm. MS: $M^{+}+1=408$ Da.

Intermediate 52: **4-(3-Furan-3-yl-5-methyl-benzyl)-3-oxo-3,4-dihydro-2H-**

25 **benzo[1,4]-oxazine-6-carbaldehyde**. To a solution of intermediate 51 (0.15 g, 0.368 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.017 g, 0.014 mmol) was added furan-3-boronic acid (0.045 g, 0.405 mmol) followed by Na_2CO_3 (2.0 mL, 2.0 M solution). The solution was then heated to reflux overnight with good stirring. The heat was

turned off, the solution was poured into H₂O (30 mL), and the aqueous phase was extracted with CH₂Cl₂ (3 × 40 mL). The organic phase was then dried over MgSO₄, filtered, and concentrated down under reduced pressure. The product was chromatographed with ethyl acetate/hexane (1:3). ¹H NMR (DMSO-d₆) δ 2.24 (s, 3H), 4.95 (s, 2H), 5.15, (s, 2H), 6.87 (s, 1H), 6.94 (s, 1H), 7.19-7.20 (d, 1H), 7.30-7.32, (d, 1H), 7.47 (s, 1H), 7.69 (s, 1H), 7.55-7.56 (d, 1H), 8.10 (s, 1H), 9.76 (s, 1H) ppm. MS: M⁺+1=348 Da.

Example 115: **4-(3-Furan-3-yl-5-methyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 52.

¹H NMR (DMSO-d₆) δ 2.20-2.25 (s, 3H), 4.90-5.00 (s, 2H), 5.15-5.20 (s, 2H), 6.85-6.90 (s, 1H), 7.00-7.15 (d, 1H) 7.19-7.20, (d, 1H), 7.20-7.35 (m, 3H), 7.42-7.45 (s, 1H), 7.65-7.79 (s, 1H), 8.10-8.15 (s, 1H) ppm. MS: M⁺+1=463 Da.

Intermediate 53: **4-(3-Methyl-5-thiophene-3-yl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazine-6-carbaldehyde**. The title compound was synthesized in a manner similar to intermediate 52 from intermediate 51 and thiophene-3-boronic acid.

Example 116: **4-(3-Methyl-5-thiophene-3-yl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The compound was synthesized in a manner analogous to Example 1 from intermediate 53. ¹H NMR (DMSO-d₆) δ 2.32 (s, 3H), 4.95 (s, 2H), 5.16(s, 2H), 7.05-7.08 (d, 1H), 7.12-7.14 (d, 2H), 7.23-7.25, (d, 1H), 7.39-7.41 (d, 1H), 7.46-7.47 (d, 3H), 7.55-7.56 (s, 1H), 7.77 (s, 1H) ppm. MS: M⁺+1=479 Da.

Intermediate 54: **4-[3-(3,5-Dimethyl-isoxazol-4-yl)-5-methyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazine-6-carbaldehyde**. The title compound was synthesized in a manner similar to intermediate 52 from intermediate 51 and 3,5-dimethylisoxazol-4-boronic acid.

Example 117: **4-[3-(3,5-Dimethyl-isoxazol-4-yl)-5-methyl-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 54. ¹H NMR (DMSO-d₆) δ 2.07 (s, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 4.92 (s, 2H), 5.18 (s, 2H), 7.01-7.16, (m, 5H), 7.22-7.24 (d, 1H), 7.47 (s, 1H) ppm. MS: M⁺+1=492 Da.

Example 118: **3-Methyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl-benzoic acid methyl ester**. ¹H NMR (DMSO-d₆) δ 2.35 (s, 3H), 3.80 (s, 3H), 4.94 (s, 2H), 5.22 (s, 2H), 7.05 (s, 1H), 7.15-7.17 (d, 1H), 7.26-7.28 (d, 1H), 7.41 (s, 1H), 7.50 (s, 1H), 7.68 (d, 1H) ppm. MS: M⁺+1=455 Da.

Intermediate 55: **4-(3-Methyl-5-thiazol-2-yl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazine-6-carbaldehyde**. The title compound was synthesized in a manner similar to intermediate 52 from intermediate 51 and 2-tributyltinthiazole.

Example 119: **4-(3-Methyl-5-thiazol-2-yl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 55. ¹H NMR (DMSO-d₆) δ 2.36 (s, 3H), 4.94 (s, 2H), 5.23 (s, 2H), 7.13-7.16 (d, 2H), 7.25 (s, 2H), 7.40-7.50, (b, 1H), 7.70 (t, 3H), 7.86 (s, 1H) ppm. MS: M⁺+1=480 Da.

Intermediate 56: **3-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-5-methyl-benzonitrile**. The title compound was synthesized in a manner similar to intermediate 28 from intermediate 51 and zinc cyanide.

Example 120: **3-Methyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl-benzonitrile**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 56. ¹H NMR (DMSO-d₆) δ 2.37 (s, 3H), 4.96 (s, 2H), 5.18 (s, 2H),

6.94 (s, 1H), 7.14-7.16, (d, 1H), 7.25-7.26 (d, 1H), 7.50 (s, 1H), 7.54-7.57 (d, 3H) ppm. MS: $M^+ + 1 = 422$ Da.

Intermediate 57: **4-(3-Methyl-5-pyrazin-2-yl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazine-6-carbaldehyde**. To a solution of intermediate 51 (0.150 g,

5 0.368 mmol) and $\text{Pd(PPh}_3)_4$ in dry DMF (15 mL) was added

2-tributylstannylpyrazine (0.025 g, 0.04 mmol) followed by CuI (0.014 g, 0.07 mmol). The solution was heated to reflux and monitored by TLC. The heat was turned off and the solution was filtered through celite. The solution was then concentrated down under reduced pressure, dissolved in CH_3CN and extracted

10 with hexane (5×30 mL). The organic phase was dried over MgSO_4 , filtered, and concentrated down under reduced pressure. The product was chromatographed with ethyl acetate/hexane (1:3). ^1H NMR (DMSO-d_6) δ 2.35 (s, 3H), 4.98 (s, 2H), 5.26 (s, 2H), 7.20-7.22 (d, 2H), 7.52-7.56 (m, 2H), 7.84-7.90 (d, 2H), 8.59 (s, 1H), 8.68 (s, 1H), 9.19 (s, 1H), 9.78 (s, 1H) ppm. MS: $M^+ + 1 = 360$ Da.

15 Example 121: **4-(3-Methyl-5-pyrazin-2-yl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 57.

^1H NMR (DMSO-d_6) δ 2.38 (s, 3H), 4.97 (s, 2H), 5.25 (s, 2H), 7.08 (s, 1H), 7.14-7.16 (s, 2H), 7.26 (s, 2H), 7.47 (s, 1H), 7.88-7.91 (d, 1H), 8.57 (s, 1H), 8.67 (s, 20 1H), 9.20 (s, 1H) ppm. MS: $M^+ + 1 = 475$ Da.

Intermediate 58: **4-[3-(4-Methoxy-phenyl)-propyl]-3-oxo-chrom-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 4 using intermediate 3 and 1-(3-iodo-propyl)-4-methoxy-benzene.

Example 122: **4-[3-(4-Methoxy-phenyl)-propyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. ^1H NMR (DMSO-d_6) δ 1.85 (t, 25 2H), 2.60 (t, 2H), 3.91, (t, 2H), 4.72 (s, 2H), 6.81-6.83 (d, 2H), 7.12, (t, 3H), 7.13-7.14 (d, 1H), 7.35 (s, 1H), 7.66 (s, 1H) ppm. MS: $M^+ + 1 = 441$ Da.

Example 123: **5-{4-[3-(4-Methoxy-phenyl)-propyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. ¹H NMR (DMSO-d₆) δ 1.84 (t, 2H), 2.448 (t, 2H), 3.69, (t, 3H), 3.90 (s, 2H), 4.70 (s, 2H), 6.81-6.83 (d, 2H), 7.11-7.13 (m, 4H), 7.20, (s, 1H), 7.34 (s, 1H), 7.80 (s, 1H) ppm. MS: M⁺+1=425 Da.

Example 124: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[3-(3,4,5-trimethoxy-phenyl)-propyl]-4H-benzo[1,4]oxazin-3-one**. ¹H NMR (DMSO-d₆) δ 1.92 (t, 2H), 2.62 (t, 2H), 3.58, (s, 3H), 3.71 (s, 6H), 3.97 (t, 2H), 4.71 (s, 2H), 6.49 (s, 1H), 7.11-7.13 (d, 2H), 7.21-7.22 (d, 1H), 7.44 (s, 1H), 7.66 (s, 1H) ppm. MS: M⁺+1=501 Da.

Example 125: **5-{4-[3-(4-Methoxy-phenyl)-propyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. ¹H NMR (DMSO-d₆) δ 1.92 (t, 2H), 2.61 (t, 2H), 3.58 (s, 3H), 3.71 (s, 6H), 3.95 (t, 2H), 4.70 (s, 2H), 6.49 (s, 2H), 7.12-7.14 (d, 1H), 7.22-7.23 (d, 1H), 7.43 (s, 1H), 7.82 (s, 1H) ppm. MS: M⁺+1=485 Da.

Example 126: **Acetic acid 2,6-dimethyl-4-{3-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-methyl}-phenyl ester**. ¹H NMR (DMSO-d₆) δ 2.06 (s, 6H), 2.28 (s, 3H), 4.93 (s, 2H), 5.10 (s, 2H), 7.05-7.08 (d, 3H), 7.15 (d, 1H), 7.25-7.29 (d, 1H), 7.51 (s, 1H) ppm. MS: M⁺+1=469 Da.

Example 127: **4-[3-(2,3-Dichloro-phenyl)-propyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. ¹H NMR (DMSO-d₆) δ 1.89 (t, 2H), 2.68 (t, 2H), 3.93 (t, 2H), 4.71 (s, 2H), 7.12-7.13 (d, 1H), 7.21 (t, 2H), 7.41 (s, 1H), 7.50 (s, 2H), 7.69 (s, 1H) ppm. MS: M⁺+1=480 Da.

Example 128: **4-(5-*tert*-Butyl-2-methyl-2H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. ¹H NMR (DMSO-*d*₆) δ 1.15 (s, 9H), 3.79 (s, 3H), 4.88 (s, 2H), 5.18 (s, 2H), 5.97 (s, 2H), 7.17-7.19 (d, 1H), 7.22-7.23(d, 1H), 7.32 (s, 1H), 7.60 (s, 1H) ppm. MS: M⁺+1=443 Da.

Example 129: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[2-(4-phenoxy-phenyl)-ethyl]-4H-1,4-benzoxazin-3-one**. MP=220-224°C. MS: M⁺-1=487.1 Da.

Example 130: **4-[2-(3,5-Dimethoxy-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MP=267-269°C. MS: M⁺+1=457.0 Da.

Intermediate 59: **4-[2-(4-*tert*-Butyl-phenyl)-ethyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 4 using intermediate 3, potassium iodide, and 1-(4-*t*-butyl-phenyl)-2-bromoethane.

Example 131: **4-[2-(4-*tert*-Butyl-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]-oxazin-3-one**. The title compound was prepared in a manner analogous to Example 1 from intermediate 59. MP=283-285°C. MS: M⁺+1=453.2 Da.

Example 132: **4-[2-(4-Dimethylamino-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]-oxazin-3-one**. MP=266-268°C. MS: M⁺+1=440.1 Da.

Intermediate 60: **Methanesulfonic acid 2-(3,4-difluoro-phenyl)-ethyl ester**. To a solution of 2-(3,4-difluoro-phenyl)-ethanol (1.00 g, 6.33 mmol) in tetrahydrofuran (63.0 mL) at 0°C was added triethylamine (1.95 mL, 13.9 mmol) followed by methanesulfonyl chloride (0.538 mL, 6.96 mmol). The solution was allowed to warm to room temperature overnight, quenched with water (20 mL), and diluted with ethyl acetate (100 mL). The layers were separated and the

aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with saturated NaHCO₃ (1 × 20 mL), brine (1 × 20 mL), dried over MgSO₄, filtered, and concentrated to give the title compound.

¹H NMR (CDCl₃) δ 2.92 (s, 3H), 3.01 (t, J=6.59 Hz, 2H), 4.37-4.40 (m, 2H),
5 6.94-6.97 (m, 1H), 7.03-7.06 (m, 1H), 7.07-7.15 (m, 1H) ppm. ¹⁹F NMR (CDCl₃) δ -140.48, -137.71 ppm.

Intermediate 61: **4-[2-(3,4-Difluoro-phenyl)-ethyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. To a solution of intermediate 3 (0.500 g, 2.82 mmol) in dry DMF (28.0 mL) at 0°C was added dropwise potassium
10 bis(trimethylsilyl)amide (5.64 mL, 2.82 mmol). After 25 minutes, a solution of intermediate 60 (1.48 g, 6.26 mmol) in DMF (2 mL) was added dropwise. The solution was warmed to room temperature over 18 hours, diluted with water (30 mL), ethyl acetate (50 mL), and acidified with 1N HCl. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL).
15 The combined organic extracts were washed with brine (1 × 20 mL), dried over MgSO₄, filtered, and concentrated to give the title compound. The compound was purified by silica gel flash column chromatography (25% ethyl acetate/hexanes, then 20% acetone/hexanes) to afford a white solid. ¹H NMR (DMSO-d₆) δ 2.84-2.88 (m, 2H), 4.17-4.20 (m, 2H), 4.71 (s, 2H), 7.16 (d, J=8.06 Hz),
20 7.24-7.40 (m, 3H), 7.55-7.66 (m, 1H), 9.89 (s, 1H) ppm. ¹⁹F NMR (CDCl₃) δ -142.55, -139.55 ppm. MS: M⁺+1=318.1 Da.

Example 133: **4-[2-(3,4-Difluoro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 from intermediate 61. MP=263-
25 266°C. MS: M⁺-1=432.1 Da.

Example 134: **4-[2-(4-Chloro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MP=278-280°C. MS: M⁺-1=430.0 Da.

Example 135: **4-[2-(3-Chloro-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 131. MP=280-282°C. MS: $M^+-1=430.0$ Da.

5 Example 136: **4-[2-(4-Methoxy-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 131. ^1H NMR (DMSO- d_6) δ 2.79-2.83 (m, 2H), 3.69 (s, 3H), 4.05-4.09 (m, 2H), 4.70 (s, 2H), 6.83 (d, $J=8.55$ Hz, 1H), 7.16 (d, $J=8.55$ Hz, 1H), 7.19 (d, $J=8.79$ Hz, 2H), 7.21-7.24 (m, 1H), 7.45 (d, $J=1.71$ Hz, 1H), 7.69 (s, 1H), 13.80 (bs, 1H) ppm. MS: $M^++1=427.0$ Da.

10 Example 137: **4-[2-(3-Methoxy-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 131. MP=233-236°C. MS: $M^+-1=426.1$ Da.

15 Example 138: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(2-p-tolyl-ethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 131. MP=267-269°C. MS: $M^+-1=410.2$ Da.

Example 139: **4-Ethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: $M^++1=383.0$.

20 Example 140: **4-(4-Methyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. Microanalysis ($\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$): calculated: C=60.59%, H=4.07%, N=7.07%, O=12.11%, S=16.17%; found: C=60.30%, H=4.16%, N=6.91%. MS: $M^+-1=395.1$ Da.

25 Intermediate 62: **2-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-acetamide**. The title compound was synthesized as in intermediate 4 using intermediate 3 (0.200 g, 1.13 mmol), and 2-bromoacetamide (0.233 g, 1.69 mmol) and a catalytic amount of sodium iodide. MS: $M^++1=235.1$ Da.

Example 141: **2-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro benzo[1,4]oxazin-4-yl]-acetamide**. The title compound was synthesized

in a manner analogous to Example 1 using intermediate 62. MS: $M^+ + 1 = 348.1$ Da.

5 Example 142: **4-(3-Methyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo [1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 141. Microanalysis ($C_{20}H_{16}N_2O_3S_2$): calculated: C=60.59%, H=4.07%, N=7.07%, O=12.11%, S=16.17%; found: C=60.35%, H=4.36%, N=6.70%. MS: $M^+ - 1 = 395.1$ Da.

10 Example 143: **4-Cyclohexylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 141. Microanalysis ($C_{19}H_{20}N_2O_3S_2$): calculated: C=58.74%, H=5.19%, N=7.21%, O=12.35%, S=16.51%; found: C=58.49%, H=5.27%, N=7.13%. MS: $M^+ + 1 = 389.2$ Da.

15 Example 144: **4-(3-Methyl-butyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. Microanalysis ($C_{17}H_{18}N_2O_3S_2$): calculated: C=56.33%, H=5.01%, N=7.73%, O=13.24%, S=17.69%; found: C=55.70%, H=4.77%, N=7.54%. MS: $M^+ - 1 = 361.2$ Da.

Example 145: **4-Cyclopropylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: $M^+ - 1 = 345.1$ Da.

20 Example 146: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-thiophen-3-ylmethyl-4H-benzo[1,4]oxazin-3-one**. MS: $M^+ - 1 = 387.1$ Da.

25 Intermediate 63: **3-Oxo-4-pyridin-2-ylmethyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. To a solution of DMF and intermediate 3 (0.300 g, 2.03 mmol) was added sodium hydride (0.085 g, 3.54 mmol) and 3-(bromomethyl)pyridine hydrobromide (0.470 g, 1.85 mmol). The reaction stirred at room temperature for 24 hours. The DMF was removed in vacuo, and the reaction mixture was diluted with ethyl acetate, washed with $NaHCO_3$, and

brine. The organic layer was dried with magnesium sulfate and concentrated.

MS: $M^+ + 1 = 269.2$ Da.

Example 147: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-pyridin-2-ylmethyl-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized as in

5 Example 1 using intermediate 63. MS: $M^+ + 1 = 384.2$ Da.

Example 148: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-pyridin-4-ylmethyl-4H-benzo[1,4]oxazin-3-one**. MS: $M^+ + 1 = 384.2$ Da.

Example 149: **3-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-benzonitrile**. MS: $M^+ - 1 = 406.2$ Da.

10 Example 150: **4-(3,5-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: $M^+ - 1 = 409.2$ Da.

Example 151: **4-Biphenyl-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. MS: $M^+ - 1 = 457.2$ Da.

15 Example 152: **(S)-2-Methyl-4-naphthalen-2-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 18. MS: $M^+ - 1 = 447.1$ Da.

20 Example 153: **4-Benzyl-8-methoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized as in Example 2 using intermediate 10 and rhodanine. MS: $M^+ - 1 = 411.0$ Da.

Example 154: **8-Methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized as in Example 1 using intermediate 20. MS: $M^+ - 1 = 305.1$ Da.

25 Examples 155-188 were synthesized in a synthesized in a manner analogous to Example 38.

Example 155: **4-(3,3-Dimethyl-butyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=377.52$ Da.

Example 156: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-trifluoromethoxy-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=467.47$ Da.

5 Example 157: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-trifluoromethyl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=451.47$ Da.

Example 158: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-trifluoromethyl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=451.47$ Da.

10 Example 159: **4-Biphenyl-2-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=459.57$ Da.

Example 160: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-phenyl-propyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=411.53$ Da.

Example 161: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-phenoxy-propyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=427.53$ Da.

15 Example 162: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-styryl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=485.61$ Da.

Example 163: **4-(4-Benzyloxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=489.6$ Da.

20 Example 164: **4-(3-Difluoromethoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=449.48$ Da.

Example 165: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-trifluoromethylsulfanyl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=483.53$ Da.

Example 166: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(2-trifluoromethoxy-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=467.47$ Da.

Example 167: **4-(4-Methoxy-3-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=481.5$ Da.

5 Example 168: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-trifluoromethylsulfanyl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=483.53$ Da.

10 Example 169: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(2-trifluoromethylsulfanyl-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=483.53$ Da.

Example 170: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-phenoxy-benzyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=475.57$ Da.

15 Example 171: **4-Bicyclo[2.2.1]hept-5-en-2-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=399.52$ Da.

Example 172: **3-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzamide**. MS: $M^++1=426.5$ Da.

Example 173: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(2-phenyl-propyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=411.53$ Da.

20 Example 174: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-phenyl-butyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=425.56$ Da.

Example 175: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(5-phenyl-pentyl)-4H-1,4-benzoxazin-3-one**. MS: $M^++1=439.59$ Da.

25 Example 176: **4-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzamide**. MS: $M^++1=426.5$ Da.

Example 177: **N-{4-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-phenyl}-acetamide**. MS: $M^{+}+1=440.53$ Da.

5 Example 178: **4-(3,4-Dichloro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=452.35$ Da.

Example 179: **4-(4-Chloro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=417.91$ Da.

Example 180: **4-Benzyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=383.47$ Da.

10 Example 181: **4-(3,5-Dimethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=411.53$ Da.

Example 182: **4-(4-Methoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=413.5$ Da.

15 Example 183: **4-(4-Nitro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=428.47$ Da.

Example 184: **4-(4-*tert*-Butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=439.59$ Da.

20 Example 185: **4-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=519.47$ Da.

Example 186: **4-(2-Dibenzofuran-3-yl-2-oxo-ethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^{+}+1=501.56$ Da.

Example 187: **4-(3-Fluoro-5-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^+ + 1 = 469.46$ Da.

5 Example 188: **4-Naphthalen-2-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. MS: $M^+ + 1 = 433.53$ Da.

10 Intermediate 64: **5-Bromo-2-chloro-3-nitropyridine**. In DMF (40 mL) was stirred 5-bromo-3-nitro-2-pyridinol (8.76 g, 40 mmol) and the solution treated dropwise with phosphorus oxychloride (28 mL). The solution warmed to 80° for 5 hours. The mixture was cooled to room temperature and carefully poured into a mixture of ice and water (400 mL). This mixture was stirred overnight to precipitate. The solid was collected by filtration, washed with water (2 × 100 mL) and dried at 65°C on the high vacuum line for 3 hours to give the title compound. MS: $M^+ - 1 = 237.9$ Da.

15 Intermediate 65: **(5-Bromo-3-nitropyridin-2-yloxy)acetic acid methyl ester**. A solution of methylglycolate (1.62 g, 18 mmol) in THF (30 mL) was treated with NaH (0.48 g, 20 mmol) and stirred at 0°C for 0.5 hours. This solution was then added via syringe to a solution of intermediate 64 (3.0 g, 12.6 mmol) in THF (30 mL) and stirred at room temperature, overnight. The mixture was evaporated at reduced pressure until free of THF. The residue was partitioned between ethyl acetate (110 mL) and water (100 mL). The organic phase was separated and washed with brine (100 mL) and then dried over magnesium sulfate. The solvents were evaporated at reduced pressure to give a yellow solid which was purified by MPLC (40 g silica gel column, 7:3 [hexane/ethyl acetate]). The appropriate fractions were combined and evaporated at reduced pressure to give the title compound as a white solid. MS: $M^+ + 1 = 292.9$ Da.

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Intermediate 66: **7-Bromo-1H-pyrido[2,3-b][1,4]oxazin-2-one**. In concentrated hydrochloric acid (8 mL) was stirred intermediate 65 (1.0 g, 3.43 mmol) which was then cooled to 0°C. This was then treated, in parts, with tin dust (0.92 g, 7.8 mmol) and then warmed to 80°C for 1 hour. The mixture was cooled to room

temperature and diluted with water (100 mL). The mixture was stirred to form a precipitate. The solid was collected by filtration, washed with water (10 mL), and dried at 65°C for 3 hours under a vacuum to give the title compound. MS:

$M^{+}+1=230.9$ Da.

5 Intermediate 67: **1-Benzyl-7-bromo-1H-pyrido[2,3-b][1,4]oxazin-2-one**. In DMF (30 mL) was stirred intermediate 66 (650 mg, 2.83 mmol) and cesium carbonate (3.9 g, 12 mmol). To this was added, dropwise, benzyl bromide (513 mg, 3.0 mmol) and the mixture was stirred overnight at room temperature. The mixture was filtered free of insolubles and the DMF was evaporated at
10 reduced pressure to give a crude oil which was purified by MPLC (90 g silica gel column, 9:1 (methylene chloride/ethyl acetate). The appropriate fractions were combined and evaporated at reduced pressure to give the title compound. MS: $M^{+}+1=321.0$ Da.

15 Intermediate 68: **1-Benzyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carbaldehyde**. In DMF (6 mL) was stirred intermediate 67 (0.61 g, 1.9 mmol), sodium formate (272 mg, 4.0 mmol) and bis(triphenylphosphine)palladium (II) dichloride (280 mg, 0.4 mmol). The mixture was treated with a continuous stream of carbon monoxide (bubbled into the solution) and warmed to 100°C. The mixture was heated for 5 hours and then cooled to room temperature. The dark
20 solution was treated with ethyl acetate (100 mL) and sodium bicarbonate (100 mL) and filtered through celite. The organic phase was separated and dried over magnesium sulfate. The solvents were evaporated at reduced pressure to give a dark oil which was purified by MPLC (90 g silica gel column, 9:1 [methylene chloride/ethyl acetate]). The appropriate fractions were combined and evaporated
25 in vacuo to give the named product as a thick oil. MS: $M^{+}-1=268.1$ Da.

Example 189: **1-Benzyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-1H-pyrido[2,3-b][1,4]oxazin-2-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 68. Microanalysis ($C_{18}H_{13}N_3O_3S_2 \cdot 0.5$ ethylenediamine $0.5 H_2O$):

calculated: C=53.93, H=4.25, N=13.12, S=15.57; found: C=54.00, H=4.29, N=13.26, S=15.18. MS: $M^{+}-1=383$ Da.

Intermediate 69: **[Methyl-(2-nitrophenyl)-amino]acetic acid *tert*-butylester**. In acetonitrile (80 mL) was stirred sarcosine t-butyl ester-hydrochloride (10.1 g, 55.5 mmol) and triethylamine (6.57 g, 65 mmol). To this was added 2-fluoronitrobenzene (5.66 g, 40 mmol) and the mixture was stirred overnight at 50°C. The solution was evaporated at a reduced pressure until free of acetonitrile. The residue was partitioned between ether (100 mL) and water (100 mL). The ether layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated at reduced pressure to give an oil which was dried at 60°C in vacuo to remove all traces of fluoronitrobenzene. MS: $M^{+}+1=267.1$ Da.

Intermediate 70: **4-Methyl-3,4-dihydro-1H-quinoxalin-2-one**. A solution of intermediate 69 (9.2 g, 34.5 mmol) in methanol (50 mL) was treated with 20% Pd/C (1 g) and subjected to a hydrogen atmosphere at 100 psi/mole. The mixture was filtered free of catalyst and evaporated at reduced pressure to give the title compound. MS: $M^{+}+1=163.1$ Da.

Intermediate 71: **6-Bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one**. In acetic acid (250 mL) was dissolved intermediate 70 (5.1 g, 31.4 mmol), which was cooled to near 0°C. To this was added a solution of bromine (5.1 g, 32 mmol) in acetic acid (60 mL). The mixture was warmed to room temperature and stirred for 1 hour. The solution was then filtered to collect a dark solid. The solid was washed with water (3 × 150 mL) and air dried for 1 hour. The solid was stirred into concentrated ammonium hydroxide (100 mL) and filtered to collect the solid. The solid was then dried in vacuo at 65°C for 3 hours and then recrystallized from ethanol/water. The resultant tan solid was collected by filtration and dried at 65°C in vacuo for 3 hours. MS: $M^{+}+1=240.9$ Da.

Intermediate 72: **1-Methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 68 using intermediate 71. MS: $M^+ + 1 = 191.0$ Da.

5 Example 190: **4-Methyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-3,4-dihydro-1H-quinoxalin-2-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 72. Microanalysis ($C_{13}H_{11}N_3O_2S_2 \cdot 0.15 H_2O$): calculated: C=50.68, H=3.70, N=13.64, $H_2O=0.88$; found: C=50.31, H=3.70, N=13.47, $H_2O=0.68$. MS: $M^+ - 1 = 306$ Da.

10 Example 191: **4-(3,4-Dichloro-benzyl)-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{19}H_{12}Cl_2N_2O_4S \cdot 0.3 H_2O$): calculated: C=51.78, H=2.88, N=6.36, S=7.27; found: C=51.71, H=2.81, N=5.96, S=6.81. MS: $M^+ + 1 = 436.8$ Da.

15 Example 192: **4-(4-Methanesulfonyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis ($C_{20}H_{16}N_2O_5S_3$): calculated: C=52.16, H=3.50, N=6.08, S=20.89; found: C=51.99, H=3.51, N=5.98, S=20.65. MS: $M^+ - 1 = 459.9$ Da.

20 Example 193: **4-(4-Methanesulfonyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one, potassium salt**. In methanol (10 mL) was stirred Example 192 (502 mg, 1.1 mmol) and the mixture was treated with a solution of potassium hydroxide (0.498N) in methanol (2.18 mL, 1.1 mmol). The mixture was warmed to reflux, cooled, and evaporated to dryness. The residue was then triturated with ether (50 mL) and the resultant solid collected by filtration. ($C_{20}H_{15}N_2O_5S_3K \cdot 0.1 H_2O$): calculated: C=47.99, H=3.06, N=5.60, $H_2O=0.36$; found: C=47.82, H=2.78, N=5.55, $H_2O=0.27$. MS: $M^+ + 1 = 461.0$ Da.

25 Example 194: **4-(4-Chloro-3-trifluoromethylbenzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one, potassium salt**. 4-(4-Chloro-3-trifluoromethylbenzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one was synthesized in a manner similar to that described

for Example 2. The potassium salt of 4-(4-Chloro-3-trifluoromethylbenzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one was generated in a manner similar to that of Example 193 with methanol and KOH. Microanalysis ($C_{20}H_{12}F_3ClN_2O_3S_2$): calculated: C=49.54, H=2.49, N=5.78, S=13.22; found: C=49.60, H=2.41, N=5.74, S=13.05. MS: $M^+ + 1 = 484.9$ Da.

Example 195: **7-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-1H-pyrido[2,3-b][1,4]oxazin-2-one**. The title compound was synthesized in an analogous manner to Example 190. Microanalysis ($C_{11}H_7N_3O_3S_2 \cdot 0.2 H_2O \cdot 0.5 MeOH$): calculated: C=44.13, H=3.03, N=13.43, H_2O =1.15; found: C=44.00, H=3.03, N=13.05, H_2O =1.02. MS: $M^+ - 1 = 292.0$ Da.

Example 196: **4-(4-Chloro-3-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 84. Microanalysis ($C_{20}H_{12}F_3ClN_2O_4S \cdot 0.2 H_2O$): calculated: C=50.84, H=2.64, N=5.93; found: C=50.83, H=2.43, N=5.88. MS: $M^+ + 1 = 468.9$ Da.

Example 197: **1-Benzyl-4-methyl-7-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-3,4-dihydro-1H-quinoxalin-2-one**. The title compound was synthesized in a manner analogous to Example 190. Microanalysis ($C_{20}H_{17}N_3O_2S_2$): calculated: C=60.74, H=4.33, N=10.62; found: C=60.54, H=4.21, N=10.48. MS: $M^+ - 1 = 394.0$ Da.

Example 198: **4-(3,4-Dichloro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzothiazin-3-one**. The title compound was synthesized in an analogous manner to Example 81. Microanalysis ($C_{19}H_{12}Cl_2N_2O_2S_3 \cdot 0.15 H_2O$): calculated: C=48.54, H=2.64, N=5.96, S=20.46, H_2O =0.57; found: C=48.41, H=2.43, N=5.80, S=20.44, H_2O =0.43. MS: $M^+ - 1 = 468.9$ Da.

Example 199: **4-(3,4-Dichlorobenzyl)-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-benzo[1,4]thiazin-3-one**. The title compound was

synthesized in a manner analogous to Example 84 using intermediate 94.

Microanalysis ($C_{19}H_{12}Cl_2N_2O_3S_2$): calculated: C=50.56, H=2.68, N=6.21, S=14.21; found: C=50.36, H=2.85, N=5.82, S=13.95. MS: $M^+-1=451.9$ Da.

Example 200. **6-(5-Oxo-2-thioxo-imidazolidin-4-ylidenemethyl)-4H-**

5 **benzo[1,4]oxazin-3-one.** The title product was synthesized in a manner analogous to Example 84, except that thiohydantoin was substituted for 2-thioxoxazolid-4-one. Microanalysis ($C_{12}H_9N_3O_3S \cdot 0.85 H_2O$): calculated: C=49.60, H=3.71, N=14.46, S=10.67; found: C=49.57, H=3.18, N=13.80, S=10.40. MS: $M^+-1=274.0$ Da.

10 Intermediate 73: **4-(2,6-Di-*tert*-butylpyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde.** To a solution of intermediate 3 (1.0 g, 5.6 mmol) in N,N-dimethylformamide was added cesium carbonate (5.5 g, 16.8 mmol) and 3,5-di-*tert* butyl-bromomethyl pyridine (1.75 g, 6.7 mmol). The resulting mixture was stirred overnight. The solids were collected by filtration
15 and discarded. The filtrate was concentrated, and the residue was taken up in ethyl acetate. The organic layer was washed with 0.1N HCl, 50 mL water, and 25 mL of brine. The organic layer was dried with magnesium sulfate and concentrated to give a brown oil. Chromatography of the oil with 3:1 hexane/ethyl acetate results in a yellow oil, which was used as is. MS: $M^++1=381.2$ Da.

20 Example 201: **4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** The title compound was synthesized in a manner analogous to Example 84 using intermediate 73. MS: $M^++1=480.2$ Da. Microanalysis ($C_{26}H_{29}N_3O_4S$): calculated: C=65.11, H=6.09, N=8.76; found: C=66.57, H=6.58, N=8.13.

25 Example 202: **5-(4-Benzyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-thiazolidine-2,4-dione.** The title compound was synthesized in a manner analogous to Example 201 using thiazolidinedione in place of rhodanine. MS: $M^++1=367.0$ Da. Microanalysis ($C_{19}H_{14}N_2O_4S \cdot 0.72 H_2O$): calculated: C=60.16, H=4.10, N=7.38; found: C=60.16, H=3.90, N=7.52.

Example 203: **5-(3-Oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-oxazolidine-2,4-dione**. To 20 mL of anhydrous THF at -78° was added dropwise 11.2 mL of TiCl₄ (1.0 M in dichloromethane, 11.2 mmol). A mixture of intermediate 3 (1.0 g, 5.6 mmol) and thiooxazolidinone (1.0 g, 8.5 mmol) was added all at once, and the resulting mixture was stirred. The reaction was allowed to warm to 0°C and anhydrous pyridine (2.0 mL, 24.7 mmol) was added to the stirring mixture dropwise. Upon addition of the pyridine, the mixture was warmed to room temperature. The reaction was then refluxed for 3 hours, then maintained at 70°C overnight. The reaction was cooled and diluted with water. The resulting precipitate was collected by filtration and dried under vacuum. The resulting solid was suspended in absolute ethanol and Hunig's base (0.15 mL, 0.8 mmol) and iodomethane (0.07 mL, 1.1 mmol) were added. The reaction was stirred overnight. Concentrated HCl (2 mL) was added, and the mixture was stirred for another 3 hours. The ethanol was removed under reduced pressure, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was dried with magnesium sulfate and concentrated. The brown residue was triturated with ethyl ether, yielding a brown powder. MS: M⁺+1=261.0 Da. Microanalysis (C₁₂H₈N₂O₅·0.74 H₂O): calculated: C=52.69, H=3.49, N=10.24; found: C=52.79, H=3.25, N=9.85.

Example 204: **4-Methyl-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4a,8a-dihydro-4H-benzo[1,4]oxazin-3-one, potassium salt**. The title compound was prepared in a manner analogous to Example 84 using intermediate 4. The potassium salt was generated by treating 4-methyl-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4a,8a-dihydro-4H-benzo[1,4]oxazin-3-one in methanol with a solution of KOH in methanol (0.498N, 0.34 mL). The solution was stirred until a cloudy mixture had formed. Approximately half of the methanol was removed under reduced pressure, and the precipitate was collected by filtration and dried under vacuum. Microanalysis (C₁₃H₉N₂O₄SK·0.96 H₂O): calculated: C=45.17, H=3.18, N=8.10; found: C=45.16, H=3.08, N=7.91.

Example 205: **4-(2-Chloro-6-methoxy-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. ¹H NMR (DMSO-d₆) δ 3.81 (s, 3H), 4.93 (s, 2H), 5.12 (s, 2H), 6.77 (s, 1H), 6.97 (s, 1H), 7.04 (s, 1H), 7.14-7.16, (d, 1H), 7.23-7.25 (d, 1H), 7.50-7.55 (s, 1H) ppm. MS: M⁺+1=448 Da.

Example 206: **4-(2,6-Dimethoxy-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazine-3-one**. ¹H NMR (DMSO-d₆) δ 3.80 (s, 6H), 4.91 (s, 2H), 5.07 (s, 2H), 6.28 (s, 2H), 6.94 (s, 1H), 7.12-7.14 (d, 1H), 7.22-7.24 (d, 1H), 7.48 (s, 1H) ppm. MS: M⁺+1=444 Da.

Example 207: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(4-trifluoromethyl-benzyloxy)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 88. MP>300°C. MS: M⁺-1=465.0 Da.

Example 208: **4-Cyclohexylmethoxy-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 88. MP=249-250°C. MS: M⁺-1=403.1 Da.

Example 209: **4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethoxy)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 88. MP>300°C. MS: M⁺-1=510.1 Da.

Example 210: **4-(3,5-Diisopropyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 1.13 (d, 12H), 2.81 (m, 1H), 4.91 (s, 2H), 5.12 (s, 2H), 6.97 (s, 3H), 7.14 (d, 1H), 7.25 (d, 1H), 7.50 (s, 1H). MS: M⁺-1=466.1 Da.

Example 211: **4-(3-*tert*-Butyl-5-methyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was

synthesized in a manner analogous to Example 38. Microanalysis:

C₂₄H₂₄N₂O₃S₂ calculated: C=63.69, H=5.34, N=6.19; found: C=63.69, H=5.34,

5 N=6.09. MS: M⁺-1=452.1 Da.

Intermediate 74: **4-(3-*tert*-Butyl-5-hydroxymethyl-benzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbaldehyde**. The title compound was synthesized in a

manner analogous to intermediate 5 using intermediate 36. MS: M⁺-1=353.3 Da.

Example 212: **4-(3-*tert*-Butyl-5-hydroxymethyl-benzyl)-6-(4-oxo-2-thioxo-**

10 **thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 74.

¹H NMR (DMSO-d₆) δ 1.23 (s, 9H), 4.41 (d, 2H), 4.90 (s, 2H), 5.07 (s, 1H), 5.17 (s, 2H), 6.95 (s, 1H), 7.13-7.24 (m, 4H), 7.30 (s, 1H), 7.47 (s, 1H). MS:

M⁺-1=468.1 Da.

15 Intermediate 75: **(6-Formyl-3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid**. The title compound was synthesized in a manner analogous to Example 3 using intermediate 5. MS: M⁺-1=234.1 Da.

Intermediate 76: **4-[2-(3,5-Dimethyl-piperidin-1-yl)-2-oxo-ethyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was

20 synthesized in a manner analogous to intermediate 32 using intermediate 75 and 3,5-dimethyl-piperidine. MS: M⁺-1=330.1 Da.

Example 213: **4-[2-(3,5-Dimethyl-piperidin-1-yl)-2-oxo-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-1,4-benzoxazin-3-one**. The title

25 compound was synthesized in a manner analogous to Example 1 using intermediate 76. Microanalysis: C₂₁H₂₃N₃O₄S₂ calculated: C=56.61, H=5.20, N=9.43; found: C=56.28, H=5.31, N=9.15. MS: M⁺-1=444.1 Da.

Example 214: **4-{2-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-yl]-acetyl}-piperazine-1-carboxylic acid *tert*-butyl**

ester. The title compound was synthesized in a manner analogous to Example 213. ¹H NMR (DMSO-d₆) δ 1.41 (s, 9H), 3.37 (bs, 2H), 3.48-3.49 (m, 4H), 3.60 (bs, 2H), 4.80 (s, 2H), 4.91 (s, 2H), 6.98 (d, 1H), 7.15 (d, 1H), 7.29-7.32 (q, 1H), 7.58 (s, 1H), 13.79 (bs, 1H). MS: M⁺-1=517.1 Da.

5 Example 215: **4-(2-Oxo-2-piperazin-1-yl-ethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**

The title compound was synthesized in a manner analogous to Example 213.

¹H NMR (DMSO-d₆) δ 3.15 (bs, 2H), 3.26 (bs, 2H), 3.67 (bs, 2H), 3.81 (bs, 2H), 4.80 (s, 2H), 4.94 (s, 2H), 7.12 (s, 1H), 7.16 (d, 1H), 7.24 (d, 1H), 7.58 (s, 1H).

10 MS: M⁺-1=417.1 Da.

Intermediate 77: **3-tert-Butyl-5-(6-formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzamide.** The title compound was synthesized in a manner analogous to intermediate 32 using intermediate 31 and ammonium hydroxide.

MS: M⁺-1=366.2 Da.

15 Example 216: **3-tert-Butyl-5-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzamide.** The title compound was synthesized in a manner analogous to Example 1 using intermediate 77. ¹H NMR (DMSO-d₆) δ 1.26 (s, 9H), 4.90 (s, 2H), 5.20 (s, 2H), 7.14 (d, 2H), 7.21 (d, 1H), 7.29 (s, 1H), 7.43 (d, 2H), 7.59 (s, 1H), 7.76 (s, 1H),
20 7.93 (s, 1H). MS: M⁺-1=481.2 Da.

Example 217: **4-(3,5-Dibromo-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** The title compound was synthesized in a manner analogous to Example 38. Microanalysis: C₁₉H₁₂Br₂N₂O₃S₂ calculated: C=42.24, H=2.24, N=5.19; found: C=42.20, H=2.48, N=5.32. MS:
25 M⁺-1=538.9 Da.

Example 218: **4-[1-(3,5-Dimethyl-phenyl)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ

1.71 (d, 3H), 2.27 (s, 6H), 4.81-4.95 (dd, 2H), 6.24 (q, 1H), 6.74 (d, 1H), 6.90 (s, 1H), 6.97 (s, 2H), 7.15 (d, 1H), 7.29-7.32 (dd, 1H), 7.41 (s, 1H), 13.62 (bs, 1H).
MS: $M^+-1=423.1$ Da.

5 Example 219: **5-[4-(3,5-Di-*tert*-butyl-4-hydroxy-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. Microanalysis: $C_{27}H_{30}N_2O_5S_1$ calculated: C=65.57, H=6.11, N=5.66; found: C=65.28, H=6.13, N=5.51. MS: $M^+-1=493.3$ Da.

10 Example 220: **4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. 1H NMR (DMSO- d_6) δ 1.26 (s, 18H), 5.04 (s, 2H), 5.18 (s, 2H), 6.86 (s, 1H), 7.07 (s, 2H), 7.32 (d, 1H), 7.50 (s, 1H). MS: $M^+-1=513.2$ Da.

15 Example 221: **4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-8-methyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 35 using BEMP resin as in intermediate 22. 1H NMR (DMSO- d_6) δ 1.25 (s, 8H), 2.24 (s, 3H), 4.95 (s, 2H), 5.15 (s, 2H), 6.92 (s, 1H), 7.07 (s, 2H), 7.17 (s, 1H), 7.47 (s, 1H). MS: $M^+-1=509.2$ Da.

20 Example 222: **4-[3-*tert*-Butyl-5-(4-methyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. 1H NMR (DMF- d_7) δ 1.24 (s, 9H), 2.69 (s, 3H), 2.71-2.76 (bs, 4H), 2.81-2.93 (bs, 4H), 3.63 (s, 2H), 4.93 (s, 1H), 5.30 (s, 2H), 7.11-7.21 (m, 3H), 7.24 (s, 1H), 7.29 (s, 1H), 7.37 (s, 1H). MS: $M^+-1=550.2$ Da.

25

Intermediate 78: **4-(4-Bromomethyl-benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a

manner analogous to intermediate 16 using intermediate 10 and α,α' -dibromo-*p*-xylene. MS: $M^+-1=374.0$ Da.

Intermediate 79: **2-Methyl-4[4-(4-methyl-piperazin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 17 using intermediate 78 and 1-methylpiperazine. MS: $M^+-1=393.2$ Da.

Example 223: **2-Methyl-4-[4-(4-methyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 79. ^1H NMR (DMF- d_7) δ 1.59 (d, 3H), 2.71-2.76 (bs, 4H), 2.90-3.02 (bs, 4H), 3.57 (s, 2H), 4.99-5.04 (dd, 1H), 5.20-5.37 (dd, 2H), 7.15-7.24 (m, 2H), 7.32-7.38 (m, 2H). MS: $M^+-1=508.1$ Da.

Example 224: **5-[4-(2,6-Di-*tert*-butyl-pyridin-4-ylmethyl)-8-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 35 using thiazoladinedione instead of rhodanine. ^1H NMR (DMSO- d_6) δ 1.24 (s, 18H), 2.23 (s, 3H), 4.94 (s, 2H), 5.14 (s, 2H), 6.90 (s, 1H), 7.06 (s, 2H), 7.17 (s, 1H), 7.60 (s, 1H). MS: $M^+-1=492.2$ Da.

Example 225: **4-(2,6-Dichloro-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ^1H NMR (DMSO- d_6) δ 4.96 (s, 2H), 5.20 (s, 2H), 7.02 (s, 1H), 7.17-7.26 (dd, 2H), 7.51 (s, 1H), 7.57 (s, 2H). MS: $M^+-1=450.9$ Da.

Example 226: **5-[4-(2,6-Dichloro-pyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. ^1H NMR (DMSO- d_6) δ 4.89

(s, 2H), 5.18 (s, 2H), 7.05 (d, 1H), 7.15 (s, 1H), 7.29 (d, 1H), 7.50 (s, 2H), 8.09 (s, 1H). MS: $M^+-1=434.1$ Da.

5 Example 227: **5-(3-Oxo-4-pyridin-4-ylmethyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. ^1H NMR (DMSO- d_6) δ 4.89 (s, 2H), 5.16 (s, 2H), 7.01 (s, 1H), 7.13 (d, 1H), 7.19-7.21 (dd, 1H), 7.28 (d, 2H), 7.60 (s, 1H), 8.46 (d, 2H). MS: $M^+-1=366.0$ Da.

10 Example 228: **5-{4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66, using BEMP resin and intermediate 3 to provide 4-[4-(4-methyl-piperazine-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde. 4-[4-(4-Methyl-piperazine-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde was then reacted with 1-methylpiperazine in a manner analogous to
15 intermediate 17 to provide 4-[4-(4-methyl-piperazine-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbaldehyde which was then reacted thiazoladinedione in an analogous manner to Example 66. ^1H NMR (DMSO- d_6) δ 2.35 (s, 3H), 2.63-2.81 (bs, 4H), 3.13-3.30 (bs, 4H), 3.43 (s, 2H), 4.83 (s, 2H), 5.12 (s, 2H), 7.05-7.15 (m, 3H), 7.23-7.29 (m, 5H). MS: $M^+-1=477.1$ Da.

20 Example 229: **4-(2,6-Dimethyl-pyridin-4-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ^1H NMR (DMSO- d_6) δ 2.46 (s, 6H), 4.92 (s, 2H), 5.10 (s, 2H), 6.89 (s, 1H), 6.99 (s, 2H), 7.14 (d, 1H), 7.25 (d, 1H), 7.41 (s, 1H). MS: $M^+-1=410.0$ Da.

25 Example 230: **5-[4-(2,6-Dimethyl-pyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 66. Microanalysis:

$C_{20}H_{17}N_3O_4S_1$ calculated: C=60.75, H=4.33, N=10.63; found: C=60.66, H=4.59, N=10.82. MS: $M^+ + 1 = 394.1$ Da.

5 Example 231: **5-Methoxy-2-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-pyrimidine-4-carboxylic acid methyl ester**. The title compound was synthesized in a manner analogous to Example 38. 1H NMR (DMSO- d_6) δ 3.82 (s, 3H), 3.88 (s, 3H), 4.81 (s, 2H), 5.23 (s, 2H), 7.12-7.20 (m, 3H), 7.45 (s, 1H), 8.75 (s, 1H). MS: $M^+ - 1 = 471.0$ Da.

10 Example 232: **4-(4,6-Dimethyl-pyrimidine-2-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. 1H NMR (DMSO- d_6) δ 2.37 (s, 3H), 4.85 (s, 2H), 5.24 (s, 2H), 6.95 (s, 1H), 7.15-7.16 (m, 2H), 7.28 (d, 1H), 7.47 (s, 1H). MS: $M^+ - 1 = 412.0$ Da.

15 Example 233: **4-(4-Chloro-3-trifluoromethyl-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38 using intermediate 24 instead of intermediate 3. Microanalysis: $C_{20}H_{11}Cl_1N_2O_3S_2$ calculated: C=47.77, H=2.20, N=5.57; found: C=47.67, H=2.07, N=5.54. MS: $M^+ - 1 = 501.9$ Da.

20 Example 234: **4-(4,6-Di-*tert*-butyl-pyrimidin-2-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis: $C_{25}H_{28}N_4O_3S_2$ calculated: C=60.46, H=5.68, N=11.28; found: C=58.45, H=5.47, N=10.80. MS: $M^+ - 1 = 496.1$ Da.

25 Example 235: **4-(4,6-Di-*tert*-butyl-pyrimidin-2-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38 using intermediate 24.

Microanalysis: C₂₅H₂₇N₄O₃S₂F₁ calculated: C=58.35, H=5.29, N=10.89;
found: C=58.31, H=4.88, N=10.79. MS: M⁺-1=514.1 Da.

5 Example 236: **4-[3-*tert*-Butyl-5(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38 using intermediate 24. Microanalysis: C₂₆H₂₇N₂O₄S₂F₁ calculated: C=60.68, H=5.29, N=5.44; found: C=60.72, H=5.31, N=5.42. MS: M⁺-1=514.1 Da.

10 Example 237: **4-[3-*tert*-Butyl-5(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 1.22 (s, 9H), 1.33 (s, 6H), 4.89 (m, 3H), 5.16 (s, 2H), 7.14-7.24 (m, 5H), 7.36 (s, 1H), 7.51 (s, 1H). MS: M⁺-1=495.1 Da.

15 Example 238: **4-[4-(3-Aza-spiro[5.5]undec-3-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4*H*-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMSO-d₆) δ 1.15-1.60 (m, 12H), 3.31 (bs, 4H), 4.19 (bs, 2H), 4.89 (s, 2H), 5.21 (s, 2H), 6.96-7.16 (m, 4H), 7.40-7.45 (m, 4H). MS: M⁺+1=548.2 Da.

20 Example 239: **5-{4-[4-(3-Aza-spiro[5.5]undec-3-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 19 using thiazolidinedione instead of rhodanine. ¹H NMR (DMSO-d₆) δ 1.25-1.45 (m, 12H), 2.70 (bs, 4H), 3.89 (bs, 2H), 4.88 (s, 2H), 5.18 (s, 2H), 7.07-7.19 (m, 4H), 7.34-7.37 (m, 4H). MS: M⁺+1=532.3 Da.

25 Example 240: **4-{4-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzyl}-piperazine-1-carboxylic acid ethyl ester**. The title compound was synthesized in a manner analogous to Example 239. ¹H NMR (DMSO-d₆) δ 1.15 (t, 3H), 2.32 (bs, 4H), 3.47 (s, 2H),

4.01 (q, 2H), 4.91 (s, 2H), 5.16 (s, 2H), 7.11-7.16 (m, 2H), 7.23-7.7 (m, 4H), 7.63 (s, 1H). MS: $M^+ + 1 = 537.2$ Da.

Example 241: **4-{4-[3-Oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl]-benzyl}-piperazine-1-carboxylic acid**

5 **ethyl ester**. The title compound was synthesized in a manner analogous to Example 19. ^1H NMR (DMSO- d_6) δ 1.12 (t, 3H), 2.45 (bs, 4H), 3.31 (bs, 4H), 3.61 (s, 2H), 4.01 (q, 2H), 4.91 (s, 2H), 5.18 (s, 2H), 7.07 (s, 1H), 7.14 (d, 1H), 7.24 (d, 1H), 7.30 (s, 4H), 7.41 (s, 1H). MS: $M^+ + 1 = 553.2$ Da.

Intermediate 80: **4-(3-Chloro-propyl)-8-fluoro-3-oxo-3,4-dihydro-2H-**

10 **benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 16 using intermediate 3 and 3-bromo-1-chloropropane.

Intermediate 81: **8-Fluoro-4-(3-morpholin-4-yl-propyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a

15 manner analogous to intermediate 17 using intermediate 80 and morpholine.

Example 242: **8-Fluoro-4-(3-morpholin-4-yl-propyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1 using intermediate 81.

20 ^1H NMR (DMSO- d_6) δ 1.90 (quint, 2H), 2.81 (bs, 4H), 3.66 (bs, 4H), 4.00 (t, 2H), 4.81 (s, 2H), 7.11 (d, 1H), 7.22 (d, 1H), 7.37 (s, 1H), 7.41 (s, 1H). MS: $M^+ + 1 = 430.0$ Da.

Example 243: **8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-(3-piperidin-1-yl-propyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was

25 synthesized in a manner analogous to Example 242. ^1H NMR (DMSO- d_6) δ 1.40-1.78 (m, 6H), 2.02 (m, 2H), 3.08 (bm, 4H), 3.98 (t, 2H), 4.81 (s, 2H), 7.03 (d, 1H), 7.18 (s, 2H). MS: $M^+ + 1 = 436.1$ Da.

Example 244: **4-[3-(3,5-Dimethyl-piperidin-1-yl)-propyl]-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title

compound was synthesized in a manner analogous to Example 242. ¹H NMR (DMSO-d₆) δ 0.75 (4, 1H), 0.86 (d, 6H), 0.93-0.95 (bm, 1H), 1.68-1.79 (m, 2H), 2.01-2.03 (m, 2H), 2.47-2.50 (m, 2H), 2.98-3.10 (m, 2H), 3.29-3.35 (m, 3H), 3.97-4.00 (m, 2H), 4.81 (s, 1H), 6.97-7.02 (m, 1H), 7.14-7.15 (m, 2H). MS:

5 M⁺+1=464.1 Da.

Example 245: **4-(3-Diisopropylamino-propyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 242. ¹H NMR (DMF-d₄) δ 1.34 (d, 6H), 2.19-2.40 (m, 2H), 3.34-3.40 (m, 2H), 3.65-3.81 (m, 2H), 4.13 (t, 10 3H), 4.59 (s, 2H), 7.12 (d, 1H), 7.24 (s, 2H). MS: M⁺+1=452.1 Da.

Example 246: **5-[4-(3,4-Dichloro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 2, with the substitution of thiazoladinedione for rhodanine. ¹H NMR (DMSO-d₆) δ 12.50 (s, 1H), 7.67 (s, 15 1H), 7.65 (s, 1H), 7.61 (d, 1H), 7.29 (d, 1H), 7.24 (d, 1H), 7.16 (d, 1H), 7.10 (s, 1H), 5.16 (s, 2H), 4.91 (s, 2H). MS: M⁺-1=434.9 Da.

Example 247: **4-(3,5-Di-*tert*-butyl-benzyl)-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 84. ¹H NMR (CDCl₃/CD₃OD 3 drop) δ 7.44 20 (d, 2H), 7.22 (2, 2H), 7.07 (s, 2H), 7.06 (d, 1H), 6.42 (s, 1H), 5.17 (s, 2H), 1.20 (s, 9H). MS: M⁺-1=479.20 Da.

Example 248: **Acetic acid 4-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-phenyl ester**. Microanalysis: C₂₁H₁₆N₂O₅S₂; calculated: C=57.26, H=3.66, N=6.36; found: 25 C=57.35, H=3.75, N=6.49. MS: M⁺+1=441.1 Da.

Example 249: **5-[4-(4-Benzyloxy-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was

synthesized in a manner analogous to Example 246. Microanalysis:

$C_{26}H_{20}N_2O_5S$; calculated: C=66.09, H=4.27, N=5.39; found: C=66.10, H=4.18, N=5.75. MS: $M^+ - 1 = 471.2$ Da.

5 Example 250: **4-(3,5-Di-*tert*-butyl-cyclohexylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in an analogous manner to Example 2 using intermediate 3 and 3,5-Di-*t*-butyl-1-(bromomethyl)cyclohexane. Microanalysis:
 $C_{27}H_{36}N_2O_3S_2 \cdot 0.14 H_2O$; calculated: C=64.44, H=7.27, N=5.57, KF(H_2O)=0.49; found: C=64.56, H=7.22, N=5.69, KF(H_2O)=0.51. MS:
10 $M^+ + 1 = 384.2$ Da.

Example 251: **5-{4-[3-Methyl-5-(4-methyl-piperazin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in an analogous manner to Example 19 using 2,4-thiazolidinedione in place of rhodanine. Microanalysis: $C_{26}H_{28}N_4O_4S \cdot 0.7$
15 H_2O ; calculated: C=61.81, H=5.87, N=11.09; found: C=61.67, H=5.63, N=10.90. MS: $M^+ + 1 = 493.2$ Da.

Example 252: **5-{3-Oxo-4-[3-(propane-2-sulfonyl)-benzyl]-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 2 using thiazoladinedione instead
20 of rhodanine. Microanalysis: $C_{22}H_{20}N_2O_6S_2$; calculated: C=55.92, H=4.27, N=5.93; found: C=55.89, H=4.16, N=5.76. MS: $M^+ + 1 = 473.1$ Da.

Example 253: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-[3-(propane-2-sulfonyl)-benzyl]-4H-1,4-benzoxazin-3-one**. Microanalysis:
 $C_{22}H_{20}N_2O_5S_3$; calculated: C=54.08, H=4.13, N=5.73; found: C=54.07,
25 H=3.95, N=5.58. MS: $M^+ + 1 = 489.1$ Da.

Example 254: **4-(3-Isopropylsulfanyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis: $C_{22}H_{20}N_2O_3S_3$;

calculated: C=57.87, H=4.42, N=6.14; found: C=57.61, H=4.07, N=5.91. MS: $M^+ + 1 = 457.1$ Da.

Example 255: **4-[3-Methyl-5-(4-methyl-piperazin-1-ylmethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.**

5 Microanalysis: $C_{26}H_{28}N_4O_3S_2 \cdot 0.2 H_2O$; calculated: C=60.96, H=5.59, N=10.94, KF(H_2O)=0.70; found: C=60.78, H=5.55, N=10.97, KF(H_2O)=0.56. MS: $M^+ + 1 = 493.2$ Da.

Example 256: **3-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-N,N-dimethyl-benzenesulfonamide.** The title compound was synthesized in a manner analogous to Example 252.

10 Microanalysis: $C_{21}H_{19}N_3O_6S_2$; calculated: C=53.27, H=4.04, N=8.87; found: C=52.86, H=3.71, N=8.80. MS: $M^+ + 1 = 474.1$ Da.

Example 257: **4-[3-(Morpholine-4-sulfonyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** Microanalysis:

15 $C_{23}H_{21}N_3O_6S_3$; calculated: C=51.96, H=3.98, N=7.90; found: C=51.98, H=3.70, N=7.90. MS: $M^+ + 1 = 532.0$ Da.

Example 258: **5-(4-Cyclohexylmethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-thiazolidine-2,4-dione.** The title compound was synthesized in a manner analogous to Example 252. Microanalysis: $C_{19}H_{20}N_2O_4S \cdot 0.17 H_2O$;

20 calculated: C=60.77, H=5.46, N=7.46; found: C=60.40, H=5.30, N=7.34. MS: $M^+ - 1 = 371.1$ Da.

Example 259: **4-[4-(Morpholine-4-sulfonyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** Microanalysis:

25 $C_{23}H_{21}N_3O_6S_3$; calculated: C=51.96, H=3.98, N=7.90; found: C=51.76, H=3.98, N=7.90. MS: $M^+ - 1 = 531.0$ Da.

Example 260: **4-(3-Isopropyl-2-methoxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one.** Microanalysis:

$C_{23}H_{22}N_2O_4S_2 \cdot 0.5 H_2O$; calculated: C=59.59, H=5.00, N=6.04; found:

C=59.61, H=5.16, N=5.84. MS: $M^+ + 1 = 455.0$ Da.

Example 261: **4-Cyclohexylmethyl-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title product was synthesized in

5 a manner analogous to Example 84. Microanalysis: $C_{19}H_{20}N_2O_4S \cdot 0.2 H_2O$; calculated: C=60.68, H=5.42, N=7.45; found: C=60.62, H=5.27, N=7.37. MS: $M^+ + 1 = 373.1$ Da.

Example 262: **N,N-Dimethyl-3-[3-oxo-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-1,4-benzoxazin-4-ylmethyl]-benzenesulfonamide**.

10 Microanalysis: $C_{21}H_{19}N_3O_5S_3 \cdot 0.05 H_2O$; calculated: C=51.42, H=3.92, N=8.57, KF(H_2O)=0.18; found: C=51.30, H=3.66, N=8.71, KF(H_2O)=0.20. MS: $M^+ + 1 = 490.1$ Da.

Example 263: **4-(3-*tert*-Butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. Microanalysis: $C_{23}H_{22}N_2O_3S_2 \cdot 0.1$

15 H_2O ; calculated: C=62.73, H=5.08, N=6.36, KF(H_2O)=0.40; found: C=62.44, H=4.97, N=6.48, KF(H_2O)=0.10. MS: $M^+ + 1 = 439.0$ Da.

Example 264: **N,N-Dimethyl-4-{3-oxo-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl}-benzenesulfonamide**. Microanalysis: $C_{21}H_{19}N_3O_5S_2 \cdot 0.1 H_2O$; calculated:

20 C=51.33, H=3.94, N=8.55, KF(H_2O)=0.37; found: C=50.98, H=3.93, N=8.39, KF(H_2O)=0.39. MS: $M^+ + 1 = 490.0$ Da.

Example 265: **5-[1-[4-(3-Methanesulfonyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 252.

25 Microanalysis: $C_{20}H_{16}N_2O_6S_2 \cdot 0.05 H_2O$; calculated: C=53.93, H=3.64, N=6.29, KF(H_2O)=0.20; found: C=53.97, H=3.54, N=6.29, KF(H_2O)=0.17. MS: $M^+ + 1 = 445.0$ Da.

Example 266: **4-Benzyl-6-{1-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidene]-ethyl}-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 2 using 6-acetyl-4H-benzo[1,4]oxazin-3-one instead of intermediate 3. Microanalysis: $C_{20}H_{16}N_2O_3S_2$; calculated: C=60.59, H=4.07, N=7.07; found: C=60.30, H=3.90, N=6.97. MS: $M^++1=397.0$ Da.

Example 267: **7-[4-Oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-1-phenethyl-1H-pyrido[2,3-b][1,4]oxazin-2-one**. The title compound was synthesized in a manner analogous to Example 190. Microanalysis: $C_{19}H_{15}N_3O_3S_2$; calculated: C=57.42, H=3.80, N=10.57, S=16.13; found: C=57.35, H=3.74, N=10.41, S=15.77. MS: $M^++1=397.0$ Da.

Example 268: **6-{1-[4-Oxo-2-thioxo-thiazolidin-(5Z)-ylidene]-ethyl}-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 266. Microanalysis: $C_{13}H_{10}N_2O_3S_2 \cdot 0.1 H_2O$; calculated: C=50.66, H=3.34, N=9.09, $KF(H_2O)=0.58$; found: C=50.31, H=3.17, N=9.24, $KF(H_2O)=0.49$. MS: $M^++1=306.9$ Da.

Example 269: **8-Fluoro-4-(3-methanesulfonyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 2 using intermediate 24. Microanalysis: $C_{20}H_{15}FN_2O_5S_3$; calculated: C=50.20, H=3.16, N=5.85; found: C=50.19, H=3.29, N=5.72. MS: $M^+-1=477.9$ Da.

Example 270: **4-(3-Methanesulfonyl-benzyl)-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. Microanalysis: $C_{20}H_{16}N_2O_5S_3$; calculated: C=52.16, H=3.50, N=6.08; found: C=52.07, H=3.44, N=6.02. MS: $M^+-1=461.0$ Da.

Example 271: **4-(3,5-Bis-trifluoromethyl-benzyl)-6-[4-oxo-2-thioxo-oxazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 84. 1H NMR

(DMSO- d_6) δ 4.94 (s, 2H), 5.29 (s, 2H), 6.68 (s, 1H), 7.18 (d, 1H), 7.51 (s, 1H), 7.55 (d, 1H), 7.99 (s, 3H). MS: $M^+ + 1 = 503.0$ Da.

5 Example 272: **5-[1-[4-(3,5-Bis-trifluoromethyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 2, using ammonium acetate and 2,4-thiazolidinedione instead of rhodanine and EDDA. Microanalysis ($C_{21}H_{12}F_6N_2O_4S$): calculated: C=50.21, H=2.41, N=5.58; found: C=50.51, H=2.24, N=5.38. MS: $M^+ - 1 = 501.1$ Da.

10 Example 273: **4-(3,5-Bis-trifluoromethyl-benzyl)-8-fluoro-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{21}H_{11}N_2F_7O_3S_2$): calculated: C=47.02, H=2.07, N=5.22; found: C=46.88, H=1.83, N=5.29. MS: $M^+ - 1 = 535.1$ Da.

15 Example 274: **4-[3-*tert*-Butyl-5-(2-methoxy-ethoxymethoxymethyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. Microanalysis ($C_{28}H_{32}N_2O_6S_2$): calculated: C=60.41, H=5.79, N=5.03; found: C=60.22, H=5.69, N=4.85. MS: $M^+ - 1 = 556.2$ Da.

20 Example 275: **4-[3-*tert*-Butyl-5-(morpholine-4-carbonyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 59. Microanalysis ($C_{29}H_{32}N_4O_4S_2 \cdot 0.25 C_2H_8N_2$): calculated: C=60.40, H=5.51, N=8.65; found: C=58.8, H=5.50, N=9.03. MS: $M^+ - 1 = 550.2$ Da.

25 Example 276: **5-[1-{4-[3-*tert*-Butyl-5-(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-meth-(Z)-ylidene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 272 using intermediate 24. 1H NMR (DMSO- d_6) δ 1.28

(s, 9H), 1.32 (s, 6H), 4.88-4.89 (m, 1H), 4.98 (s, 2H), 5.15 (s, 2H), 7.00-7.36 (m, 5H), 7.61 (s, 1H). MS: $M^+ - 1 = 497.1$ Da.

Example 277: 5-[1-[4-(3-*tert*-Butyl-5-morpholin-4-yl)methyl-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione.

5 The title compound was synthesized in a manner analogous to Example 19, using 1,3-bis-bromomethyl-5-*tert*-benzene and morpholine, and using ammonium acetate and 2,4-thiazolidinedione instead of rhodanine and EDDA. ^1H NMR (DMSO- d_6) δ 1.22 (s, 9H), 2.26 (bs, 4H), 3.43-3.45 (m, 6H), 4.88 (s, 2H), 5.17 (s, 2H), 6.95 (s, 1H), 7.12-7.27 (m, 5H), 7.58 (s, 1H).

10 **Example 278: 4-(3-*tert*-Butyl-5-morpholin-4-yl)methyl-benzyl)-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 19. ^1H NMR (DMSO- d_6) δ 1.23 (s, 9H), 2.46-2.48 (bs, 4H), 3.52 (bs, 4H), 3.64 (bs, 2H), 4.88 (s, 2H), 5.18 (s, 2H), 7.02 (s, 1H), 7.10-7.13 (m, 2H), 7.19 (d, 1H), 7.21 (s, 1H),
15 7.33 (d, 1H). Microanalysis ($\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_4\text{S}_2$): calculated: C=62.55, H=5.81, N=7.81; found: C=62.58, H=5.00, N=7.17.

Example 279: 4-[3-*tert*-Butyl-5-(4-methyl-piperazine-1-carbonyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one.

The title compound was synthesized in a manner analogous to Example 59.

20 ^1H NMR (DMSO- d_6) δ 1.27 (9s, 9H), 2.43 (s, 3H), 2.56 (bs, 2H), 2.74 (bs, 2H), 3.28 (bs, 2H), 3.61 (bs, 2H), 4.88 (s, 2H), 5.21 (s, 2H), 7.10 (s, 1H), 7.17 (d, 1H), 7.19 (d, 1H), 7.26 (d, 2H), 7.53 (s, 1H). MS: $M^+ - 1 = 563.2$ Da.

Intermediate 81: 4-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzoic acid methyl ester. The title compound was synthesized in a
25 manner analogous to intermediate 22 using intermediate 3 and 4-bromomethyl-benzoic acid methyl ester. MS: $M^+ + 1 = 326.0$ Da.

Intermediate 82: **4-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzoic acid**. The title compound was synthesized in a manner analogous to intermediate 15 using intermediate 81. MS: $M^+-1=310.0$ Da.

5 Intermediate 83: **4-[4-(4-Methyl-piperazine-1-carbonyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 32 using intermediate 82 and 1-methylpiperazine. MS: $M^+-1=393.2$ Da.

10 Example 280: **4-[4-(4-Methyl-piperazine-1-carbonyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 83. ^1H NMR (DMSO- d_6) δ 2.73 (bs, 3H), 3.29-3.43 (m, 8H), 4.86 (s, 2H), 5.18 (s, 2H), 7.05-7.16 (m, 3H), 7.21 (s, 1H), 7.36 (s, 4H). MS: $M^+-1=507.1$ Da.

15 Example 281: **4-[4-(Morpholine-4-carbonyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 280. ^1H NMR (DMSO- d_6) δ 3.28 (bs, 4H), 3.50 (bs, 4H), 4.89 (s, 2H), 5.18 (s, 2H), 7.07 (s, 1H), 7.12 (d, 1H), 7.21 (d, 1H), 7.35 (s, 4H), 7.45 (s, 1H). MS: $M^+-1=494.1$ Da.

20 Example 282: **4-[3-(1-Hydroxy-1-methyl-ethyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine**. Microanalysis ($\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2\text{C}_2\text{H}_8\text{N}_2$): calculated: C=57.58, H=5.64, N=11.19; found: C=57.46, H=4.97, N=8.67. MS: $M^+-1=439.1$ Da.

25 Example 283: **4-[3-*tert*-Butyl-5-(1-methoxy-1-methyl-ethyl)-benzyl]-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. Microanalysis ($\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_4\text{S}_2$): calculated: C=63.50, H=5.92, N=5.49; found: C=63.33, H=5.84, N=5.42. MS: $M^+-1=509.1$ Da.

Intermediate 84: **Acetic acid 3-*tert*-butyl-5-(8-fluoro-6-formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzyl ester**. The title compound was synthesized in a manner analogous to intermediate 46 using intermediate 24 and acetic acid 3-bromomethyl-5-*tert*-butyl-benzyl ester. MS: $M^+-1=413.4$ Da.

5 Intermediate 85: **4-(3-*tert*-Butyl-5-hydroxymethyl-benzyl)-8-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 15 using intermediate 84. MS: $M^+-1=413.1$ Da.

10 Example 284: **4-(3-*tert*-Butyl-5-hydroxymethyl-benzyl)-8-fluoro-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 85. Microanalysis ($C_{24}H_{23}F_1N_2O_4S_2$): calculated: C=59.24, H=4.76, N=5.76; found: C=59.20, H=4.57, N=5.75. MS: $M^+-1=485.1$ Da.

15 Example 285: **Acetic acid 3-*tert*-butyl-5-{8-fluoro-3-oxo-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl}-benzyl ester**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 84. Microanalysis ($C_{26}H_{25}F_1N_2O_5S_2$): calculated: C=59.08, H=4.77, N=5.30; found: C=59.23, H=4.48, N=4.60. MS: $M^+-1=528.0$ Da.

20 Intermediate 86: **2-Oxo-2,3-dihydro-benzooxazole-5-carbaldehyde**. To a 0°C solution of methanol (50 mL) and 5-formyl-2-hydroxy-benzamide (Reich et al. *J. Med. Chem.*, 2000;43(9):1670-1683) (2.0 g, 12.11 mmol) was added potassium hydroxide (1.35 g, 24.22 mmol) and then iodobenzene diacetate (3.90 g, 12.11 mmol). The reaction was stirred at 0°C for 1 hour, then diluted with ethyl acetate
25 (200 mL) and carefully acidified to pH 2 with 1N HCl. The organic layer was then washed with sodium chloride (2 × 50 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. This was used in the next step without purification. MS: $M^+-1=162.0$ Da.

Intermediate 82: **3-(3,4-Dichloro-benzyl)-2-oxo-2,3-dihydro-benzooxazole-5-carbaldehyde**. The title compound was synthesized in a manner analogous to intermediate 46 using intermediate 86 and 4-bromomethyl-1,2-dichloro-benzene. MS: $M^+ + 1 = 321.9$ Da.

5 Example 286: **3-(3,4-Dichloro-benzyl)-5-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-3H-benzooxazol-2-one**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 87. Microanalysis ($C_{18}H_{10}Cl_2N_2O_3S_2$): calculated: C=49.44, H=2.30, N=6.41; found: C=49.46, H=2.20, N=6.19. MS: $M^+ - 1 = 435.9$ Da.

10 Example 287: **4-(4-Iodo-benzyl)-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis ($C_{19}H_{13}I_1N_2O_3S_2$): calculated: C=44.89, H=2.58, N=5.51; found: C=44.99, H=2.45, N=5.33. MS: $M^+ - 1 = 507.8$ Da.

15 Intermediate 88: **4-(6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl)-benzoic acid**. The title compound was synthesized in a manner analogous to intermediate 15 using intermediate 81. MS: $M^+ - 1 = 310.0$ Da.

20 Example 288: **4-{3-Oxo-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-2,3-dihydro-benzo[1,4]oxazin-4-ylmethyl}-benzoic acid; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 1, from intermediate 88. Microanalysis ($C_{20}H_{14}N_2O_5S_2 \cdot C_2H_8N_2$): calculated: C=55.25, H=3.97, N=9.20; found: C=52.59, H=4.20, N=8.87. MS: $M^+ - 1 = 425.0$ Da.

25 Example 289: **8-Fluoro-4-(4-methanesulfonyl-benzyl)-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{20}H_{15}F_1N_2O_5S_2 \cdot C_2H_8N_2$): calculated:

C=49.59, H=3.77, N=8.26; found: C=47.31, H=3.56, N=7.50. MS: $M^+-1=477.0$ Da.

Example 290: **3-Benzyl-5-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-3H-benzooxazol-2-one; compound with ethane-1,2-diamine.** The title compound was synthesized in a manner analogous to Example 286.

Microanalysis ($C_{18}H_{12}N_2O_3S_2 \cdot C_2H_8N_2$): calculated: C=57.27, H=4.05, N=10.55; found: C=57.19, H=4.01, N=10.49. MS: $M^+-1=367.0$ Da.

Example 291: **3-(4-Methanesulfonyl-benzyl)-5-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-3H-benzoxazol-2-one; compound with ethane-1,2-diamine.** The title compound was synthesized in a manner analogous to Example 286. Microanalysis ($C_{19}H_{14}N_2O_5S_3 \cdot C_2H_8N_2$): calculated: C=50.40, H=3.81, N=8.82; found: C=48.67, H=3.89, N=8.04. MS: $M^+-1=445.0$ Da.

Example 292: **8-Fluoro-4-(4-fluoro-3-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{20}H_{11}N_2O_3S_2F_5$): calculated: C=49.38, H=2.28, N=5.76; found: C=49.26, H=2.21, N=5.71. MS: $M^++1=486.1$ Da.

Example 293: **4-[3-Chloro-5-(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine.** The title compound was synthesized in a manner analogous to Example 46. 1H NMR (DMSO- d_6) δ 1.38 (s, 6H), 2.94 (s, 4H, ethylene diamine), 4.95 (s, 2H), 5.15 (s, 2H), 6.97 (s, 1H), 7.06-7.13 (m, 3H), 7.37 (t, 1H), 7.41 (d, 1H). MS: $M^+-1=492.1$ Da.

Example 294: **8-Fluoro-4-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 46. 1H NMR (DMSO- d_6) δ 1.37 (s, 6H), 4.99 (s, 2H), 5.15 (bs, 2H), 6.99 (s, 1H), 7.23-7.26 (m, 3H), 7.41 (d, 2H), 7.49 (s, 1H). MS: $M^+-1=458.1$ Da.

Example 295: **4-(3,5-Difluoro-4-hydroxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis ($C_{19}H_{12}N_2O_4S_2F_2$): calculated: C=52.53, H=2.78, N=6.45; found: C=52.41, H=2.52, N=6.09. MS: $M^+ + 1 = 435.1$ Da.

Example 296: **{5-[4-(3-Chloro-4-fluoro-benzyl)-8-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 46 using rhodanine-3-acetic acid in place of rhodanine. Microanalysis ($C_{21}H_{13}N_2O_5S_2F_2Cl_1 \cdot 0.50 C_2H_8N_2$ [ethylene diamine] $\cdot 0.08 C_1H_4O_1$): calculated: C=48.79, H=3.21, N=7.73; found: C=48.50, H=3.05, N=7.61. MS: $M^+ + 1 = 511.0$ Da.

Example 297: **4-(3,5-Dibromo-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{19}H_{11}N_2O_3S_2F_1Br_1$): calculated: C=40.88, H=1.99, N=5.02; found: C=41.15, H=1.95, N=4.88. MS: $M^+ - 1 = 556.9$ Da.

Example 298: **5-[8-Fluoro-4-(4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 46 using thiazoladinedione instead of rhodanine. Microanalysis ($C_{19}H_{12}N_2O_4S_1F_2$): calculated: C=56.72, H=3.01, N=6.96; found: C=56.46, H=2.79, N=6.76. MS: $M^+ + 1 = 403.1$ Da.

Example 299: **8-Fluoro-4-(4-methoxy-3-trifluoromethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{21}H_{14}N_2O_4S_2F_4$): calculated: C=50.60, H=2.83, N=5.62; found: C=50.47, H=2.54, N=5.62. MS: $M^+ - 1 = 498.1$ Da.

Example 300: **4-(3-Chloro-4-fluoro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{19}H_{11}N_2O_4SF_2Cl_1$): calculated: C=52.24, H=2.54, N=6.41; found: C=51.99, H=2.66, N=6.13. MS: $M^+-1=437.0$ Da.

Example 301: **8-Fluoro-4-(4-fluoro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis ($C_{19}H_{12}N_2O_3S_2F_2$): calculated: C=54.54, H=2.89, N=6.69; found: C=54.35, H=2.81, N=6.58. MS: $M^+-1=419.0$ Da.

Example 302: **8-Fluoro-4-[4-fluoro-3-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 46. 1H NMR ($DMSO-d_6$) δ 1.44 (d, 6H), 2.93 (s, 4H, ethylene diamine), 4.91 (s, 2H), 5.14 (bs, 2H), 7.00-7.10 (m, 4H), 7.14-7.18 (m, 1H), 7.61 (dd, 1H). MS: $M^+-1=476.0$ Da.

Example 303: **4-(4-Fluoro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis ($C_{19}H_{13}N_2O_3S_2F$): calculated: C=56.99, H=3.27, N=7.00; found: C=57.04, H=3.11, N=6.96. MS: $M^++1=401.0$ Da.

Example 304: **4-[4-Fluoro-3-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 38. 1H NMR ($DMSO-d_6$) δ 1.41 (s, 6H), 2.92 (s, 4H, ethylenediamine), 4.80 (s, 2H), 5.15 (bs, 2H), 6.99-7.19 (m, 6H), 7.62 (dd, 1H). MS: $M^+-1=458$ Da.

Example 305: **5-{4-[4-Fluoro-3-(1-hydroxy-1-methyl-ethyl)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 272.

Microanalysis (C₂₂H₁₉N₂O₅SF): calculated: C=59.72, H=4.33, N=6.33; found:

5 C=59.78, H=4.10, N=6.17. MS: M⁺-1=442.0 Da.

Example 306: **4-(4-Fluoro-3-methyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis

(C₂₀H₁₅N₂O₃S₂F): calculated: C=57.96, H=3.65, N=6.76; found: C=58.13,

10 H=3.63, N=6.62. MS: M⁺-1=442.0 Da.

Example 307: **4-[3-(2-Fluoro-phenoxy)-benzyl]-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-ylmethylene}-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 272 using using BEMP resin as in intermediate 22. Microanalysis (C₂₅H₁₇N₂O₅SF): calculated: C=63.02,

15 H=3.06, N=5.88; found: C=62.79, H=3.34, N=5.78. MS: M⁺+1=477.1 Da.

Example 308: **5-[4-(3-Chloro-4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione**. The title compound was synthesized in a manner analogous to Example 307. Microanalysis (C₁₉H₁₂N₂O₄SCl): calculated: C=54.49, H=2.89, N=6.69; found: C=54.51,

20 H=2.64, N=6.57. MS: M⁺+1=419.0 Da.

Example 309: **4-(3-Chloro-4-fluoro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis

(C₁₉H₁₁N₂O₃S₂F₂Cl): calculated: C=50.39, H=2.45, N=6.19; found: C=50.48,

25 H=2.30, N=6.07. MS: M⁺+1=415.0 Da.

Example 310: **8-Fluoro-4-[2-(4-fluoro-phenoxy)-ethyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis

(C₂₀H₁₄N₂O₄S₂F₂): calculated: C=53.56, H=3.15, N=6.25; found: C=53.54, H=3.18, N=6.16. MS: M⁺+1=449.0 Da.

5 Example 311: **4-(3-Chloro-4-fluoro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis (C₁₉H₁₂N₂O₃S₂FCI): calculated: C=52.47, H=2.78, N=6.44; found: C=52.39, H=2.55, N=6.18. MS: M⁺-1=433.9 Da.

10 Example 312: **4-(3,4-Difluoro-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. Microanalysis (C₁₉H₁₂N₂O₃S₂F₂): calculated: C=54.54, H=2.89, N=6.69; found: C=54.49, H=2.77, N=6.69. MS: M⁺+1=419.0 Da.

15 Example 313: **4-{3-[Bis-(2-methoxy-ethyl)-amino]-propyl}-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 19. ¹H NMR (DMSO-d₆) δ 1.92-1.95 (m, 2H), 3.05-3.27 (m 10H), 3.54-3.57 (m, 4H), 3.95-3.98 (m, 2H), 4.80 (s, 2H), 7.12 (dd, 1H), 7.24 (s, 1H), 7.39 (s, 1H). MS: M⁺+1=484.1 Da.

20 Example 314: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinoxalin-6-ylmethyl-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.90 (s, 2H), 8.09 (d, J=8.5 Hz, 1H), 8.02 (d, J=1.4 Hz, 1H), 7.82 (dd, 1H), 7.47 (s, 1H), 7.23 (dd, 1H), 7.19 (s, 1H), 7.17 (t, 1H), 5.44 (s, 2H), 4.99 (s, 2H) ppm. MS: M⁺ +1=435.1 Da.

25 Example 315: **8-Fluoro-6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinoxalin-6-ylmethyl-4H-benzo[1,4]oxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 8.89 (s, 2H), 8.09 (d, J=8.7 Hz, 1H), 7.99

(s, 1H), 7.82 (dd, 1H), 7.07 (d, J=11.2 Hz, 1H), 7.01 (s, 2H), 5.43 (s, 2H), 5.01 (s, 2H), [2.92 (s, 4H) 0.46 M of C₂H₈N₂] ppm. MS: M⁺+1=453.1Da.

Example 316: **4-(5-Chloro-thiophen-2-ylmethyl)-6-(4-oxo-3-phenyl-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38, using 3-phenyl rhodanine instead of rhodanine. ¹H NMR (DMSO-d₆) δ 7.826 (s, 1H), 7.605 (d, J=2.0 Hz, 1H), 7.565-7.475 (m, 3H), 7.401-7.376 (m, 2H), 7.328 (dd, 1H), 7.20 (d, J=8.3 Hz, 1H), 7.155 (d, J=3.9 Hz, 1H), 6.970 (d, J=3.65 Hz, 1H), 5.267 (s, 2H), 4.864 (s, 2H) ppm. MS: M⁻-1=498.0 Da.

Example 317: **4-(2,5-Dimethyl-furan-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.548 (s, 1H), 7.300 (d, J=2.0 Hz, 1H), 7.253-7.226 (dd, 1H), 7.137 (d, J=8.3 Hz, 1H), 5.812 (s, 1H), 4.891 (s, 2H), 4.803 (s, 2H), 2.268 (s, 3H), 2.100 (s, 3H) ppm. MS: M⁻-1=399.1 Da.

Example 318: **4-(2,5-Dimethyl-furan-3-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 7.69 (s, 1H), 7.263 (dd, 1H), 7.091 (s, 1H), 4.902 (s, 4H), 2.267 (s, 3H), 2.105 (s, 3H) ppm. MS: M⁻-1=417.1 Da.

Example 319: **4-(5-Chloro-thiophen-2-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 7.587 (s, 1H), 7.304 (s, 1H), 7.215 (dd, 1H), 7.135 (d, J=3.9 Hz, 1H), 6.967 (d, J=3.9 Hz, 1H), 5.248 (s, 2H), 4.934 (s, 2H), ppm. MS: M⁻-1=439.1 Da.

Example 320: **[4-Oxo-5-(3-oxo-4-thiophen-2-ylmethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-2-thioxo-thiazolidin-3-yl]-acetic acid; compound with ethane-1,2-diamine**. The title compound was synthesized in a

manner analogous to Example 38, using rhodanine-3-acetic acid instead of rhodanine. ¹H NMR (DMSO-d₆) δ 7.778 (s, 1H), 7.555 (d, J=1.9 Hz, 1H), 7.418 (dd, 1H), 7.292 (dd, 1H), 7.202 (d, J=3.42 Hz, 1H), 7.168 (d, J=8.54 Hz, 1H), 6.960 (dd, 1H), 5.35 (s, 2H), 4.8421 (s, 2H), 4.42 (s, 2H), [2.788 (s, 4H) 0.46 M of C₂H₈N₂] ppm. MS: M⁻-1=456.0 Da.

Example 321: **{5-[4-(5-Methyl-2-trifluoromethyl-furan-3-ylmethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid; compound with ethane-1,2-diamine.** The title compound was synthesized in a manner analogous to Example 320. ¹H NMR (DMSO-d₆) δ 7.723 (s, 1H), 7.329 (dd, 1H), 7.204 (dd, 2H), 6.183 (s, 1H), 5.119 (s, 2H), 4.878 (s, 2H), 4.407 (s, 2H), 2.248 (s, 3H), [2.797 (s, 4H) 0.53M of C₂H₈N₂] ppm. MS M⁻-1=511.1 Da.

Example 322: **4-(5-Chloro-thiophen-2-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.627 (s, 1H), 7.520 (d, J=1.9 Hz, 1H), 7.26 (dd, 1H), 7.17 (s, 1H), 7.149 (d, J=2.9 Hz, 1H), 6.962 (d, J=3.9 Hz, 1H), 5.244 (s, 2H), 4.839 (s, 2H) ppm. MS: M⁻-1=421.0 Da.

Example 323: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinolin-3-ylmethyl-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.930 (d, 1H), 8.243 (s, 1H) 7.988 (d, J=10.0 Hz, 1H), 7.925 (d, J=9.27 Hz, 1H), 7.690 (t, 1H) 7.585-7.544 (m, 1H), 7.251 (s, 2H), 7.139 (s, 2H), 5.391 (s, 2H), 4.930 (s, 2H), [2.953 (s, 4H) 0.30M of C₂H₈N₂] ppm. MS M⁺+1=434.1 Da.

Example 324: **4-(5-Methyl-2-trifluoromethyl-furan-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.** The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.541 (s, 1H), 7.283 (dd, 1H), 7.185 (d, J=8.6 Hz, 1H), 7.150 (d,

J=2.0 Hz, 1H), 6.164 (s, 1H), 5.105 (s, 2H), 4.866 (s, 2H), 2.242 (d, J=1.0 Hz, 3H) ppm. MS: M⁻-1=453.1 Da.

5 Example 325: **4-(1-*tert*-Butyl-5-methyl-1H-pyrazol-3-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 7.491 (s, 1H), 7.336 (dd, 1H), 7.187 (s, 1H), 5.877 (s, 1H), 4.989 (s, 2H), 4.906 (s, 2H), 2.315 (s, 3H), 1.507 (s, 9H) ppm. MS: M⁺+1=461.2 Da.

10 Example 326: **4-(1-*tert*-Butyl-5-methyl-1H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.500 (s, 1H), 7.385 (d, J=2.2 Hz, 1H), 7.267 (dd, 1H), 7.120 (d, J=8.3 Hz, 1H), 5.860 (s, 1H), 4.984 (s, 2H), 4.811 (s, 2H), 2.312 (d, J=0.5 Hz, 3H), 1.513 (s, 9H) ppm. MS: M⁻-1=441.2 Da.

15 Example 327: **4-(2-Benzyl-5-*tert*-butyl-2H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.480 (s, 1H), 7.291-7.212 (m, 4H), 7.107 (d, J=8.6 Hz, 1H), 7.057-7.036 (m, 3H), 6.094 (s, 1H), 5.376 (s, 2H), 5.046 (s, 2H), 4.737 (s, 2H), 1.170 (s, 9H) ppm. MS: M⁻-1=519.2 Da.

20 Example 328: **8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinolin-6-ylmethyl-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 8.849 (q, 1H), 8.282 (d, 1H), 8.000 (d, 1H), 7.918 (s, 1H), 7.713 (dd, 1H), 7.512-7.481 (m, 1H), 7.404 (s, 1H), 7.261 (d, 1H), 6.950 (s, 1H), 5.393 (s, 2H), 5.064 (s, 2H) ppm. MS: M⁻-1=450.1 Da.

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Example 329: **4-(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound

was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.525 (s, 1H), 7.295 (s, 1H), 7.273 (d, J=1.9 Hz, 1H), 7.118 (d, J=8.5 Hz, 1H), 5.904 (s, 1H), 4.972 (s, 2H), 4.804 (s, 2H), 3.684 (s, 3H), 2.166 (s, 3H) ppm. MS: M⁻-1=399.1 Da.

5 Example 330: **4-(5-Chloro-pyridin-3-ylmethyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 8.540 (d, J=1.7 Hz, 1H), 8.527 (d, J=1.7 Hz, 1H), 7.890 (t, J=2.1 Hz, 1H), 7.20-7.116 (m, 2H), 6.941 (s, 1H), 5.213 (s, 2H), 4.978 (s, 2H), [2.953 (s, 4H) 0.31M of C₂H₈N₂], ppm. MS: M⁻-1=434.0 Da.

10 Example 331: **4-[4-Chloro-3-(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 46. ¹H NMR (DMSO-d₆) δ 7.805.90 (d, J=2.1 Hz, 1H), 7.278 (d, J=8.1 Hz, 1H), 7.104 (dd, J=5.8 Hz, J=2.5 Hz, 2H), 7.040 (d, J=12.2 Hz, 1H), 6.970 (s, 1H), 5.146 (s, 2H), 4.917 (s, 2H), 1.539 (s, 6H), [2.953 (s, 4H) 0.31M of C₂H₈N₂] ppm. MS: M⁻-1=491.0 Da.

15 Example 332: **4-[4-Chloro-3-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one; compound with ethane-1,2-diamine**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.822 (d, J=2.2 Hz, 1H), 7.284 (d, J=8.0 Hz, 1H), 7.132 (s, 1H), 7.113-7.08 (m, 4H), 5.149 (s, 2H), 4.829 (s, 2H), 1.548 (s, 6H), [2.890 (s, 4H) 0.52M of C₂H₈N₂] ppm. MS: M⁻-1=473.1 Da.

20 Example 333: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-thiophen-2-ylmethyl-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.572 (s, 1H), 7.476 (d, J=2.0 Hz, 1H), 7.389 (dd, J=3.9 Hz, J=1.2 Hz, 1H), 7.206-7.185 (m, 2H),

7.120 d, J=8.3 Hz, 1H), 6.932-6.911 (m, 1H), 5.301 (s, 2H), 4.807 (s, 2H) ppm.

MS: M⁻-1=387.0 Da.

Example 334: **4-(5-Methyl-pyridin-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was

5 synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.327 (s, 1H), 8.286 (s, 1H), 7.539 (s, 1H), 7.495 (s, 1H), 7.216 (dd, J=6.6 Hz, J=1.9 Hz, 1H), 7.126 (d, J=8.3 Hz, 1H), 7.076 (d, J=1.9 Hz, 1H), 5.151 (s, 2H), 4.901 (s, 2H), 2.254 (s, 3H) ppm. MS: M⁺+1=398.0 Da.

Example 335: **4-(1-Isopropyl-1H-benzimidazol-5-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound

10 was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.295 (s, 1H), 7.555 (s, 1H), 7.578 (d, J=8.3 Hz, 1H), 7.439 (s, 1H), 7.236 (s, 1H), 7.223 (s, 1H), 7.166 (d, J=8.6 Hz, 1H), 7.110 (d, J=8.3 Hz, 1H), 5.252 (s, 2H), 4.905 (s, 2H), 4.710-4.643 (m, 1H), 1.462 (d, J=6.8 Hz, 6H) ppm. MS:
15 M⁺+1=465.1 Da.

Example 336: **4-(3-Isopropyl-3H-benzimidazol-5-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound

was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.279 (d, 1H), 7.683 (s, 1H), 7.549-7.517 (m, 1H), 7.422 (s, 1H), 7.224 (s, 1H),
20 7.176 (d, J=8.6 Hz, 1H), 7.110-7.053 (m, 2H), 5.287 (s, 2H), 4.897 (s, 2H), 4.698-4.665 (m, 1H), 1.468 (d, 6.6 Hz, 6H) ppm. MS: M⁺+1=465.1 Da.

Example 337: **6-(4-Oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinolin-6-ylmethyl-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a

manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 8.816 (dd, J=2.5 Hz, J=1.7 Hz, 1H), 8.258 (d, J=7.5 Hz, 1H), 7.969 (d, J=8.6 Hz, 1H), 7.879 (s, 1H),
25 7.684 (dd, J=7.1 Hz, J=1.7 Hz, 1H), 7.479-7.448 (m, 1H), 7.393 (s, 1H), 7.195 (d, J=8.6 Hz, 1H), 7.147-7.126 (m, 2H), 5.352 (s, 2H), 4.944 (s, 2H) ppm. MS:
M⁺+1=434.0 Da.

Example 338: **5-(4-Furan-3-ylmethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene)-thiazolidine-2,4-dione**. The title compound was synthesized in an analogous manner to Example 272. ¹H NMR (DMSO-d₆) δ 7.749 (s, 1H), 7.717 (s, 1H), 7.594 (t, J=1.8 Hz, 1H), 7.360 (d, J=2.0 Hz, 1H), 7.214 (dd, J=6.6 Hz, J=2.0 Hz, 1H), 7.130 (d, J=8.2 Hz, 1H), 6.420 (dd, J=1.2 Hz, 1.0 Hz, 1H), 4.971 (s, 2H), 4.810 (s, 2H) ppm. MS: M⁻-1=355.0 Da.

Example 339: **4-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.544 (s, 1H), 7.322 (d, J=1.7 Hz, 1H), 7.219 (dd, J=6.5 Hz, J=1.9 Hz, 1H), 7.165 (d, J=8.4 Hz, 1H), 5.808 (s, 1H), 5.153 (s, 2H), 4.843 (s, 2H), 3.767 (s, 3H), 2.001 (s, 3H) ppm. MS: M⁺+1=401.0 Da.

Example 340: **4-Furan-3-ylmethyl-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one**. The title compound was synthesized in a manner analogous to Example 38. ¹H NMR (DMSO-d₆) δ 7.719 (s, 1H), 7.604 (s, 1H), 7.591 (t, J=1.7 Hz, 1H), 7.377 (d, J=2.2 Hz, 1H), 7.223-7.198 (m, 1H), 7.130 (d, J=8.6 Hz, 1H), 6.425 (dd, J=1.0 Hz, J=0.7 Hz, 1H), 4.980 (s, 2H), 4.819 (s, 2H) ppm. MS: M⁻-1=371.0 Da.

Example 341: **4-(3,4-Dichloro-benzyl)-8-fluoro-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one**. The title compound was synthesized in a manner analogous to Example 46. Microanalysis (C₁₉H₁₁Cl₂FN₂O₃S₂): calculated: C=48.62, H=2.36, N=5.97; actual: C=48.57, H=2.33, N=5.94. MS: M⁺-1= 466.9 Da.

BIOLOGICAL EXAMPLE 1

PI3Kγ Protein Expression and Purification Protocol

Spodoptera frugiperda cells, grown in ESF921 media, were coinfectd with baculovirus expressing a glu-tagged p101 and baculovirus expressing an HA-tagged p110γ, at a 3:1 ratio of p101 baculovirus to p110γ baculovirus. Sf9

cells were grown to 1×10^7 total cells/mL in 10L bioreactors and harvested 48-72 hours post infection. Samples of infected cells were then tested for expression of p101/p110 γ PI3 kinase by immunoprecipitation and Western Blot analysis methods (see below).

5 To purify PI3K γ , 4 volumes of room temperature hypotonic lysis buffer (1 mM MgCl₂, 1 mM DTT, 5 mM EGTA, 1 mM Pefabloc, 0.5 μ M aprotinin, 5 μ M leupeptin, 2 μ M pepstatin, 5 μ M E64, pH 8) per gram of cell paste, was poured onto frozen cell pellets with stirring, then lysed in a nitrogen “bomb” at 400 psi (599HC T316, Parr Instrument Co, Moline, IL). NaCl was added to
10 150 mM, and sodium cholate was added to 1% and mixed for another 45 minutes. The lysates were clarified by centrifugation for 25 minutes at 14,000 rpm. The lysates were then loaded over anti-glu-linked Protein-G Sepharose beads (Covance Research Products, Richmond, CA) using 20 mL resin/50 g cell paste. The column was washed with 15 volumes of wash buffer (1 mM DTT, 0.2 mM
15 EGTA, 1 mM Pefabloc, 0.5 μ M aprotinin, 5 μ M leupeptin, 2 μ M pepstatin, 5 μ M E64, 150 mM NaCl, 1% sodium cholate, pH 8). PI3K γ was eluted with 6 column volumes of wash buffer that contain 100 μ g/mL of a peptide that competes for binding of the glu tag. The column fractions with the eluted protein (determined by taking OD₂₈₀ readings) were collected and dialyzed in 0.2 mM EGTA, 1 mM
20 DTT, 1 mM Pefabloc, 5 μ M leupeptin, 0.5% sodium cholate, 150 mM NaCl, and 50% glycerol, pH 8. The fractions were stored at -80°C until further use.

BIOLOGICAL EXAMPLE 2

G Protein Subunits Expression

25 *Spodoptera frugiperda* cells were coinfectd with baculovirus expressing a glu-tagged G protein β_1 and baculovirus expressing a G protein β_2 , at a 1:1 ratio of glu-tagged G protein β_1 baculovirus to G protein β_2 baculovirus. Sf9 cells are grown in 10 L bioreactors and harvested 48-72 hours post infection. Samples of infected cells were tested for G protein β_1/β_2 expression by Western Blot analysis, as described below. Cell lysates were homogenized and loaded onto a

column of glu-tagged beads as in Biological Example 1 and competed off the column with a glu peptide as described in Biological Example 1.

BIOLOGICAL EXAMPLE 3

Western Blot Analysis

5 Protein samples were run on an 8% Tris-Glycine gel and transferred to a 45 μ M nitrocellulose membrane. The blots were then blocked with 5% bovine serum albumin (BSA) and 5% ovalbumin in TBST (50 mM Tris, 200 mM NaCl, 0.1% Tween 20, pH 7.4) for 1 hour at room temperature, and incubated overnight at 4°C with primary antibody diluted 1:1000 in TBST with 0.5% BSA. The
10 primary antibodies for the p110 γ , p110 α , p110 β , p85 α , G protein β_1 , and G protein γ_2 subunits were purchased from Santa Cruz Biotechnology, Inc., Santa Cruz, CA. The p101 subunit antibodies were developed at Research Genetics, Inc., Huntsville, AL based on a p101 peptide antigen.

After incubation with the primary antibody, the blots were washed in
15 TBST and incubated for 2 hours at room temperature with goat-anti-rabbit HRP conjugate (Bio-Rad Laboratories, Inc., Hercules, CA, product Number 170-6515), diluted 1:10,000 in TBST with 0.5% BSA. The antibodies were detected with ECL™ detection reagents (Amersham Biosciences Corp., Piscataway, New Jersey) and quantified on a Kodak ISO400F scanner.

BIOLOGICAL EXAMPLE 4

Immunoprecipitation

20 100 μ L of cell paste from Biological Example 1 or 2 was thawed and lysed on ice with 400 μ L of hypotonic lysis buffer (25 mM tris, 1 mM DTT, 1 mM EDTA, 1 mM Pefabloc, 5 μ M leupeptin, 5 μ M E-64 (Roche), 1% Nonidet P40, pH 7.5-8). The lysate was incubated for 2 hours at room temperature with glu-
25 tagged beads (Covance Research Products, Cambridge, England, product Number AFC-115P). The beads were washed 3 times in wash buffer (20 mM Tris, pH 7.8-8, 150 mM NaCl₂, 0.5% NP40) and the protein eluted off the beads by heating in 2 times sample buffer (Invitrogen Corporation, Carlsbad, CA, product
30 Number LC1676).

BIOLOGICAL EXAMPLE 5

PI3K γ In Vitro Kinase Assay

The inhibitory properties of the compounds in Table 1 were assayed in an in vitro PI3K assay. In a 96-well polypropylene plate, each well was spotted with 2 μ L of 50 times the desired final concentration of compound in DMSO. Purified recombinant p101/p110 γ protein (0.03 μ g; \sim 2.7 nM) and G protein β_1/γ_2 subunits (0.09 μ g; \sim 57.7 nM) for each reaction was combined in the assay buffer (30 mM HEPES, 100 mM NaCl, 1 mM EGTA, and 1 mM DTT). ATP and [γ - 32 P-ATP] (0.09 μ Ci) were added to this mixture so that the final ATP concentration in the reaction was 20 μ M. Lipid micelles were formed by sonicating phosphatidylinositol-4,5-diphosphate (PIP $_2$), phosphatidylethanolamine (PE), and Na-cholate in the assay buffer for 10 minutes, adding MgCl $_2$ and incubating on ice for 20 minutes, for final concentrations of 25 μ M PIP $_2$, 300 μ M PE, 0.02% Na-cholate, and 10 mM MgCl $_2$ in the reaction. The reactions were started by adding equal volumes lipid and enzyme mixture in a total volume of 50 μ L, allowed to run for 20 minutes at room temperature, and stopped with 100 μ L 75 mM H $_3$ PO $_4$. The lipid product was transferred to a glass fiber filter plate and washed with 75 mM H $_3$ PO $_4$ several times. The presence of radioactive lipid product (PIP $_3$) was measured by adding Wallac Optiphase mix to each well and counting in a Wallac 1450 Trilux plate reader (PerkinElmer Life Sciences Inc., Boston, MA 02118). The IC $_{50}$ for each compound tested is reported in μ M in Table 1:

TABLE 1

Ex No.	IC $_{50}$ (μ M)	Ex No.	IC $_{50}$ (μ M)	Ex No.	IC $_{50}$ (μ M)
1	0.078	8	0.081	15	0.013
2	0.045	9	0.061	16	0.328
3	0.635	10	3.635	17	0.009
4	0.023	11	0.061	18	0.319
5	0.025	12	0.027	19	0.008
6	0.560	13	0.745	20	0.003
7	0.084	14	0.005	21	0.014

TABLE 1 (cont'd)

Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)
22	0.017	52	0.016	82	3.735
23	0.005	53	0.043	83	0.260
24	0.003	54	0.040	84	0.060
25	0.008	55	0.009	85	0.021
26	0.009	56	0.018	86	12.300
27	0.003	57	0.029	87	16.100
28	0.003	58	0.032	88	0.003
29	0.031	59	0.070	89	0.004
30	0.002	60	0.026	90	0.004
31	0.083	61	0.070	91	0.008
32	0.012	62	0.850	92	0.006
33	0.004	63	0.049	93	0.016
34	0.003	64	0.016	94	0.029
35	0.012	65	0.095	95	0.225
36	0.002	66	0.257	96	0.670
37	1.625	67	0.060	97	0.003
38	0.006	68	0.555	98	0.005
39	0.335	69	0.008	99	0.018
40	0.015	70	0.012	100	0.005
41	0.061	71	0.006	101	0.005
42	0.041	72	0.014	102	0.002
43	1.445	73	0.007	103	0.004
44	0.265	74	0.019	104	0.002
45	0.336	75	0.155	105	0.005
46	0.008	76	0.006	106	0.009
47	0.320	77	0.021	107	0.072
48	0.042	78	0.057	108	0.004
49	0.061	79	0.020	109	0.330
50	0.010	80	0.017	110	0.055
51	0.165	81	0.029	111	0.014

TABLE 1 (cont'd)

Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)
112	0.022	142	0.044	172	0.145
113	0.014	143	0.035	173	0.039
114	0.005	144	0.024	174	0.002
115	0.015	145	0.026	175	0.004
116	0.024	146	0.030	176	0.059
117	0.040	147	0.049	177	0.025
118	0.023	148	0.061	178	0.004
119	0.019	149	0.021	179	0.007
120	0.030	150	0.005	180	0.009
121	0.067	151	0.061	181	0.010
122	0.005	152	1.030	182	0.165
123	0.007	153	0.096	183	0.021
124	0.015	154	0.160	184	0.003
125	0.018	155	0.010	185	0.102
126	0.010	156	0.021	186	0.315
127	0.043	157	0.021	187	0.098
128	0.180	158	0.028	188	0.020
129	0.049	159	0.010	189	0.640
130	0.003	160	0.007	190	0.240
131	0.039	161	0.004	191	0.007
132	0.012	162	0.053	192	0.008
133	0.005	163	0.030	193	0.006
134	0.005	164	0.013	194	0.006
135	0.005	165	0.015	195	1.910
136	0.007	166	0.020	196	0.026
137	0.003	167	0.010	197	0.390
138	0.010	168	0.012	198	0.006
139	0.042	169	0.008	199	0.009
140	0.029	170	0.009	200	3.64
141	0.860	171	0.015	201	0.070

TABLE 1 (cont'd)

Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)
202	0.003	232	0.125	262	0.019
203	0.175	233	0.035	263	0.018
204	0.016	234	2.070	264	0.004
205	0.032	235	1.240	265	0.018
206	0.060	236	0.005	266	1.610
207	0.002	237	0.006	267	0.460
208	0.002	238	0.036	268	4.640
209	0.074	239	0.039	269	0.014
210	0.045	240	0.032	270	0.011
211	0.017	241	0.052	271	0.101
212	0.022	242	0.055	272	0.070
213	2.095	243	0.180	273	0.121
214	3.180	244	0.185	274	0.013
215	1.085	245	0.185	275	0.025
216	0.026	246	0.003	276	0.007
217	0.042	247	0.010	277	0.005
218	0.055	248	0.021	278	0.007
219	0.006	249	0.008	279	0.016
220	0.495	250	0.175	280	0.008
221	0.895	251	0.025	281	0.008
222	0.006	252	0.021	282	0.013
223	0.295	253	0.016	283	0.011
224	0.255	254	0.010	284	0.010
225	0.049	255	0.015	285	0.021
226	34.200	256	0.020	286	0.220
227	0.048	257	0.028	287	0.016
228	0.003	258	0.004	288	0.035
229	0.020	259	0.013	289	0.010
230	0.043	260	0.004	290	0.243
231	0.050	261	0.002	291	0.433

TABLE 1 (cont'd)

Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)	Ex No.	IC ₅₀ (μM)
292	0.011	309	0.002	327	0.245
293	0.015	310	0.009	328	0.006
294	0.003	311	0.001	329	0.028
295	0.004	312	0.003	330	0.047
296	3.850	313	0.035	331	0.009
297	0.036	314	0.036	332	0.007
298	0.001	315	0.044	333	0.007
299	0.006	316	3.700	334	0.025
300	0.003	317	0.021	335	0.034
301	0.001	318	0.025	336	0.009
302	0.012	319	0.005	337	0.008
303	0.002	321	9.730	338	0.012
304	0.008	322	0.003	339	0.080
305	0.016	323	0.029	340	0.013
306	0.001	324	0.033	341	0.003
307	0.005	325	0.018		
308	0.001	326	0.025		

FORMULATION EXAMPLE 1

Tablet Formulation	
Ingredient	Amount
Compound of Formula I	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

The compounds of the present invention (e.g., a compound of Formula I, or a pharmaceutically acceptable salt thereof) can be mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for treatment of a PI3K-mediated disorder or condition.

FORMULATION EXAMPLE 2

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection can be added 20.0 g of a compound of the present invention. The mixture is stirred, and the pH is adjusted to 5.5 with hydrochloric acid. The volume is adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampules, each containing 2.0 mL (40 mg of invention compound), and sealed under nitrogen. The solution is administered by injection to a subject suffering from a PI3K-mediated disorder or condition and in need of treatment.

FORMULATION EXAMPLE 3

Patch Formulation

Ten milligrams of a compound of the present invention can be mixed with 1 mL of propylene glycol and 2 mg of acrylic-based polymer adhesive containing a resinous cross-linking agent. The mixture is applied to an impermeable backing (30 cm²) and applied to the upper back of a patient for sustained release treatment of a PI3K-mediated disorder or condition.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.